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(71) Applicant (*for all designated States except US*): **SMITHKLINE BEECHAM CORPORATION** [US/US]; One Franklin Plaza, Philadelphia, PA PA (US).

(72) Inventors; and
(75) Inventors/Applicants (*for US only*): **KAZMIERSKI, Wieslaw, Mieczyslaw** [US/US]; GlaxoSmithKline, Five Moore Drive, PO Box 13398, Research Triangle Park, NC 27709 (US). **AQUINO, Christopher, Joseph** [US/US]; GlaxoSmithKline, Five Moore Drive, PO Box 13398, Research Triangle Park, NC 27709 (US). **BIFULCO, Neil** [US/US]; GlaxoSmithKline, Five Moore Drive, PO Box 13398, Research Triangle Park, NC 27709 (US). **BOROS, Eric, Eugene** [US/US]; GlaxoSmithKline, Five Moore Drive, PO Box 13398, Research Triangle Park, NC 27709 (US). **CHAUDER, Brian, Andrew** [CA/US]; GlaxoSmithKline, Five Moore Drive, PO Box 13398, Research Triangle Park, NC 27709 (US). **CHONG, Pek, Yoke** [MY/US]; GlaxoSmithKline, Five Moore Drive, PO Box 13398, Research Triangle Park, NC 27709 (US). **DUAN, Maosheng** [CN/US]; GlaxoSmithKline, Five Moore Drive, PO Box 13398, Research Triangle Park, NC 27709 (US). **DEANDA, JR., Felix** [US/US]; GlaxoSmithKline, Five Moore Drive, PO Box 13398, Research Triangle Park, NC 27709 (US). **KOBLE, Cecilia, Suarez** [VE/US]; GlaxoSmithKline, Five Moore Drive, PO Box 13398, Research Triangle Park, NC 27709 (US). **MCLEAN, Ed, Williams** [US/US]; GlaxoSmithKline, Five Moore Drive, PO Box 13398, Research Triangle Park, NC 27709 (US). **PECKHAM, Jennifer, Poole** [US/US]; GlaxoSmithKline, Five Moore Drive, PO Box 13398, Research Triangle Park, NC 27709 (US). **PERKINS, Angilique, C** [US/US]; GlaxoSmithKline, Five Moore Drive, PO Box 13398, Research Triangle Park, NC 27709 (US). **THOMPSON, James, Benjamin** [US/US]; GlaxoSmithKline, Five Moore Drive, PO Box 13398, Research Triangle Park, NC 27709 (US). **VANDERWALL, Dana** [US/US]; GlaxoSmithKline, Five Moore Drive, PO Box 13398, Research Triangle Park, NC 27709 (US).

(74) Agents: **LEVY, David, J** et al.; GlaxoSmithKline, Five Moore Drive, PO Box 13398, Research Triangle Park, NC 27709 (US).

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(54) Title: CCR5 ANTAGONISTS AS THERAPEUTIC AGENTS

(57) Abstract: The present invention relates to compounds of formula (I) or pharmaceutically acceptable derivatives thereof, useful in the treatment or prophylaxis of CCR5-related diseases and disorders, for example, in the inhibition of HIV replication, the prevention or treatment of an HIV infection, and in the treatment of the resulting acquired immune deficiency syndrome (AIDS).

CCR5 ANTAGONISTS AS THERAPEUTIC AGENTS

FIELD OF THE INVENTION

The present invention relates to a novel class of piperidine derivatives useful as antagonists of the chemokine receptor CCR5, compositions containing such compounds and methods of treating HIV infection and associated conditions. The invention also relates to methods of treatment or prophylaxis of other CCR5 mediated diseases and disorders.

BACKGROUND OF THE INVENTION

The human immunodeficiency virus ("HIV") is the causative agent for acquired immunodeficiency syndrome ("AIDS"), a disease characterized by the destruction of the immune system, particularly of $CD4^+$ T-cells, with attendant susceptibility to opportunistic infections, and its precursor AIDS-related complex ("ARC"), a syndrome characterized by symptoms such as persistent generalized lymphadenopathy, fever and weight loss.

In addition to CD4, HIV requires a co-receptor for entry into target cells. The chemokine receptors function together with CD4 as co-receptors for HIV. The chemokine receptors CXCR4 and CCR5 have been identified as the main co-receptors for HIV-1. CCR5 acts as a major co-receptor for fusion and entry of macrophage-tropic HIV into host cells. These chemokine receptors are thought to play an essential role in the establishment and dissemination of an HIV infection. Therefore, CCR5 antagonists are useful as therapeutic agents active against HIV.

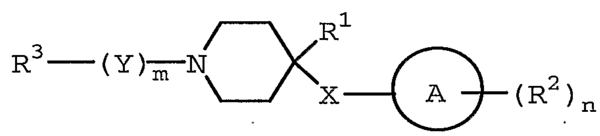
CCR5 receptors have also been reported to mediate cell transfer in inflammatory and immunoregulatory diseases and disorders such as multiple sclerosis, rheumatoid arthritis, autoimmune diabetes, chronic implant rejection, asthma, rheumatoid arthritis, Crohns Disease, inflammatory bowel disease, chronic inflammatory disease, glomerular disease, nephrotoxic serum nephritis, kidney disease, Alzheimer's Disease, autoimmune encephalomyelitis, arterial thrombosis, allergic rhinitis, arteriosclerosis,

Sjogren's syndrome (dermatomyositis), systemic lupus erythematosus, graft rejection, cancers with leukocyte infiltration of the skin or organs, human papilloma virus infection, prostate cancer, wound healing, amyotrophic lateral sclerosis, and immune mediated disorders.

There is a continued need to find new therapeutic agents to treat human diseases. CCR5 is an attractive target for the discovery of new therapeutics due to its important role in viral infections, particularly HIV infections, and other inflammatory and immune diseases and disorders.

SUMMARY OF THE INVENTION

The present invention features compounds that are CCR5 antagonists and therefore are useful in the inhibition of HIV replication, the prevention and/or treatment of infection by HIV, and in the treatment of AIDS and/or ARC. These compounds having the general formula I:



(I)

wherein R^1, R^2, R^3, X, Y, m, n and Ring A are as defined herein. The compounds of this invention may also be either pharmaceutically acceptable salts or pharmaceutical composition ingredients.

The present invention also features pharmaceutical compositions, comprising the above-mentioned compounds that are suitable for the prevention or treatment of CCR5-related diseases and conditions.

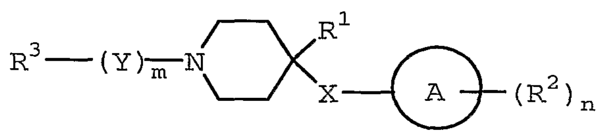
The present invention also features methods of antagonizing CCR5 chemokine receptor activity in a biological sample comprising contacting the biological sample with an effective amount of compounds of formula I or pharmaceutically acceptable derivatives or compositions thereof. The present invention also features methods of antagonizing CCR5 chemokine receptor activity in a patient comprising administering to the patient a therapeutically effective amount of compounds of formula I or pharmaceutically acceptable derivatives or compositions thereof.

The present invention further features methods of treating AIDS, methods of preventing infection by HIV, and methods of treating infection by HIV as monotherapy or in combination with other antivirals, anti-infectives, immunomodulators, antibiotics or vaccines.

The present invention further features methods of synthesizing compounds of formula I and preparing pharmaceutical compositions comprising these above-mentioned compounds.

DETAILED DESCRIPTION OF THE INVENTION

The present invention features a compound of formula (I):



(I)

or a pharmaceutically acceptable derivative thereof, wherein:

R^1 is alkyl, carbocyclyl, aryl, heterocyclyl, or heteroaryl, wherein said alkyl is optionally substituted by one or more R^7, said carbocyclyl or heterocyclyl is optionally substituted by one or more R^8 and said aryl or heteroaryl is optionally substituted by one or more R^6; or R^1 and X taken together form a saturated, partially saturated or aromatic 5-7 membered ring having 0-3 heteroatoms chosen from oxygen, sulfur, nitrogen and phosphorus that is fused to Ring A;

X is a C_{1-5} alkylene chain, wherein said C_{1-5} alkylene chain is optionally substituted by one or more groups chosen from =O, =S and halo, and wherein said C_{1-5} alkylene chain optionally contains 1-3 heteroatoms chosen from oxygen, sulfur, nitrogen and phosphorus;

each R^2 is independently chosen from $-OR^0$, $-C(O)R^0$, $-C(O)N(R^0)_2$, $-N(R^0)(-V_m-R^+)$, $-S(O)_2-R^0$, $-S(O)_2-N(R^0)_2$, $-(CH_2)_a-N(R^0)(-V_b-R^+)$, $-(CH_2)_a-(-V_b-R^+)$, halo, alkyl, aryl, carbocyclyl, heteroaryl and heterocyclyl, wherein said alkyl is optionally substituted by one or more R^7, said aryl or heteroaryl is optionally substituted by one or more R^6, and said carbocyclyl or heterocyclyl is optionally substituted by one or more R^8; or two adjacent R^2s on Ring A are optionally taken together to form a fused, saturated, partially saturated or aromatic 4-7 membered ring having 0-3 heteroatoms chosen from oxygen, sulfur, nitrogen and phosphorus; or two geminal R^2s are optionally taken together to form a spiro, saturated, partially saturated or aromatic 5-6 membered ring having 0-3 heteroatoms chosen from oxygen, sulfur and nitrogen, said fused or spiro ring being optionally substituted by one or more groups chosen from oxo, alkyl optionally substituted by one or more R^7, and aryl optionally substituted by one or more R^6;

each a is independently 0-3;

each b is independently 0 or 1;

V is alkyl, $-C(O)-$, $-S(O)_2-$, $-C(O)O-$, or $-C(O)-N(R^o)-$ (where V is attached to R^+ through the right hand side of the radical as shown hereinafter);

R^+ is alkyl, aralkyl, aryl, heteroaryl, heteroaralkyl, wherein said alkyl is optionally substituted by one or more R^7 and said aralkyl or aryl is optionally substituted by one or more R^6;

m is 0 or 1;

n is 0-5;

R^3 is H, halo, $-N(R^0)_2$, $-N(R^0)C(O)R^0$, -CN, $-CF_3$, alkyl optionally substituted by one or more groups chosen from R^7, and -S-aryl optionally substituted by $-(CH_2)_{1-6}-N(R^0)SO_2(R^0)$, carbocyclyl, aryl, heteroaryl or heterocyclyl, wherein said carbocyclyl or heterocyclyl is optionally substituted by one or more R^8, and said aryl or heteroaryl is optionally substituted by one or more R^6;

Y is $-(CR^4R^5)_p-$, $-C(O)-$, $-C(O)C(O)-$, $-C(S)-$, $-O-(CH_2)_{0-4}-C(O)-$, $-N(R^0)-C(O)-$, $-C(O)-N(R^0)-$, $-N(R^0)-C(S)-$, $-S(O)_t-$, $-O-C(=N-CN)-$,

-O-C(=N-R^0)-, -S-C(=N-CN)-, -N(R^0)-C(=N-CN)-, -C(=N-CN)-, -N(R^0)-C[=N-C(O)-R^0]-, -N(R^0)-C[=N-$S(O)_t$-R^0]-, -N(R^0)-C(=N-OR^0)-, -N(R^0)-C(=N-R^0)-, -C(=N-R^0)-, -$(CH_2)_{0-4}$-C(O)-O-, -C(=N-CN)-O-, -C(=N-R^0)-O-, or -C(=N-CN)-S- (where Y is attached to R^3 through the left hand side of the radical as shown hereinafter);

each R^4 is independently H or alkyl optionally substituted by R^7;

each R^5 is independently chosen from H, -C(O)-OR^0, aryl optionally substituted by R^6, -C(O)-OR^6, -C(O)-N$(R^0)_2$, -$S(O)_2$-N$(R^0)_2$, -$S(O)_2$-R^0, and heteroaryl optionally substituted by R^6;

p is 1-5;

t is 1 or 2;

each R^6 is independently chosen from halo, -CF_3, -OCF_3, -OR^0, -SR^0, -SCF_3, -R^0, methylenedioxy, ethylenedioxy, -NO_2, -CN, -N$(R^0)_2$, -$NR^0C(O)R^0$, -$NR^0C(O)N(R^0)_2$, -$NR^0C(S)N(R^0)_2$, -$NR^0CO_2R^0$, -$NR^0NR^0C(O)R^0$, -$NR^0NR^0C(O)N(R^0)_2$, -$NR^0NR^0CO_2R^0$, -C(O)C(O)R^0, -C(O)CH_2C(O)R^0, -CO_2R^0, -O-C(O)R^0, -C(O)R^0, -C(O)N$(R^0)_2$, -OC(O)N$(R^0)_2$, -$S(O)_tR^0$, -$S(O)_t$-OR^0, -$SO_2N(R^0)C(O)R^0$, -$NR^0SO_2N(R^0)_2$, -$NR^0SO_2R^0$, -C(=S)N$(R^0)_2$, -C(=NH)-N$(R^0)_2$, -C(=N-OR^0)-N$(R^0)_2$, -O-$(CH_2)_{0-6}$-$SO_2N(R^0)_2$, –$(CH_2)_{1-6}$NHC(O)R^0, -$SO_2N(R^0)_2$, -$(CH_2)_{1-6}$-OR^0, -$(CH_2)_{1-6}$-SR^0, -$(CH_2)_{1-6}$-CN, -$(CH_2)_{1-6}$-N$(R^0)_2$, -$(CH_2)_{1-6}CO_2R^0$, -C(O)N(R^0)N$(R^0)_2$, -C(O)N(R^0)OH, -C(O)N(R^0)SO_2R^0, -$S(O)_t$N(R^0)OR, and -$(CH_2)_{1-6}$-C(O)R^0, wherein the two R^0s on the same nitrogen optionally taken together forming a 5-8 membered saturated, partially saturated or aromatic ring having additional 0-4 ring heteroatoms chosen from oxygen, nitrogen, sulfur and phosphorus;

each R^7 is independently chosen from halogen, -CF_3, -R^0, -OR^0, -SR^0, aryl optionally substituted by R^6, -NO_2, -CN, -N$(R^0)_2$, -$NR^0C(O)R^0$, -$NR^0C(O)N(R^0)_2$, -N(R^0)C(S)N$(R^0)_2$, -$NR^0CO_2R^0$, -$NR^0NR^0C(O)R^0$, -$NR^0NR^0C(O)N(R^0)_2$, -$NR^0NR^0CO_2R^0$, -C(O)C(O)R^0, -C(O)CH_2C(O)R^0, -CO_2R^0, -C(O)R^0, -C(O)N(R^0)-N$(R^0)_2$, -C(O)N$(R^0)_2$, -C(O)$NR^0SO_2R^0$, -OC(O)N$(R^0)_2$, -$S(O)_tR^0$, -$NR^0SO_2N(R^0)_2$, -$NR^0SO_2R^0$, -C(=S)N$(R^0)_2$, -C(=NH)-N$(R^0)_2$, -$(CH_2)_{1-6}$-C(O)R^0, -$SO_2N(R^0)_2$, -OCF_3, -SCF_3, -$(CH_2)_{1-6}$-SR^0, methylenedioxy, ethylenedioxy, -$(CH_2)_{1-6}$-CN, -$(CH_2)_{1-6}$-N$(R^o)_2$,

$-S(O)_tN(R^0)OR^0$, $-(CH_2)_{1-6}-C(O)R^0$, $-C(=N-OR^0)-N(R^0)_2$, $-O-(CH_2)_{0-6}-SO_2N(R^0)_2$, and $-(CH_2)_{1-6}-NHC(O)R^0$, wherein the two R^os on the same nitrogen optionally taken together form a 5-8 membered saturated, partially saturated or aromatic ring having additional 0-4 ring heteroatoms chosen from oxygen, nitrogen, sulfur and phosphorous;

each R^8 is independently chosen from R^7, =O, =S, $=N(R^0)$, and =N(CN);

each R^0 is independently chosen from R*, -C(O)-aralkyl, $-S(O)_t$-heteroaryl, carbocyclylalkyl, aralkyl, heteroaralkyl, and heterocyclylalkyl, wherein each member of R^0 except H is optionally substituted by one or more groups chosen from R*, -OR*, $N(R^*)_2$, =O, =S, halo, $-CF_3$, $-NO_2$, -CN, -C(O)R*, $-CO_2R^*$, -C(O)-aryl, -C(O)-heteroaryl, -O-aryl, aralkyl, $-S(O)_t$-aryl, $-NR^*SO_2R^*$, -NR*C(O)R*, $-NR^*C(O)N(R^*)_2$, $-N(R^*)C(S)N(R^*)_2$, $-NR^*CO_2R^*$, -NR*NR*C(O)R*, $-NR^*NR^*C(O)N(R^*)_2$, $-NR^*NR^*CO_2R^*$, -C(O)C(O)R*, $-C(O)CH_2C(O)R^*$, $-C(O)N(R^*)N(R^*)_2$, $-C(O)N(R^*)_2$, $-C(O)NR^*SO_2R^*$, $-OC(O)N(R^*)_2$, $-S(O)_tR^*$, $-NR^*SO_2N(R^*)_2$, and $-SO_2N(R^*)_2$ wherein the two R*s on the same nitrogen optionally taken together form a 5-8 membered saturated, partially saturated or aromatic ring having additional 0-4 ring heteroatoms chosen from oxygen, nitrogen, sulfur and phosphorus; and

each R* is independently H, alkyl, cycloalkyl, aryl, heteroaryl, or heterocyclyl;

provided that when R^1 is m-methylphenyl, X is a C_2 unsubstituted saturated alkylene chain, and R^2 substituted Ring A is 4-benzyl or 4-phenyl-4'-hydroxy substituted N-piperinyl, $R^3-(Y)_m-$ is other than H, triphenylmethyl, benzoyl, 2,4-dimethoxybenzoyl, (3,5-dimethoxyphenyl)acetyl, or (3-chlorophenyl)acetyl.

As used herein, the following definitions shall apply unless otherwise indicated. The phrase "optionally substituted" is used interchangeably with the phrase "substituted or unsubstituted" or with the term "(un)substituted." Unless otherwise indicated, an optionally substituted group may have a

substituent at each substitutable position of the group, and each substitution is independent of the other.

The term “alkyl”, alone or in combination with any other term, refers to a C_{1-20} straight or branched acyclic hydrocarbon radical that is either completely saturated or contains one or more units of unsaturation. Preferably, an alkyl radical contains from one to twelve carbon atoms. More preferably, an alkyl radical contains from one to eight carbon atoms. A C_{2-20} linear or branched alkyl radical having at least one carbon-carbon double bond is also referred to as “alkenyl”. The double bond(s) of the unsaturated hydrocarbon chain may be in either the cis or trans configuration and may occur in any stable point along the chain. A C_{2-20} linear or branched alkyl having at least one carbon-carbon triple bond is also referred to as “alkynyl”. The tripe bond(s) in an alkynyl radical may occur in any stable point along the chain. The terms “alkoxy”, “hydroxyalkyl”, “alkoxyalkyl”, and “alkoxycarbonyl”, alone or in combination with any other term, include both straight and branched hydrocarbon chains.

Examples of alkyl radicals include, but are not limited to, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isoamyl, n-hexyl, ethenyl, propenyl, isopropenyl, butenyl, isobutenyl, pentenyl, hexenyl, hexadienyl, ethynyl, propynyl, butynyl, pentynyl and the like.

The term “alkoxy” refers to an alkyl ether radical (–O-alkyl). Examples of alkoxy radicals include, but are not limited to, methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, sec-butoxy, tert-butoxy and the like.

The term “cycloalkyl”, “carbocyclyl”, “carbocyclic”, “carbocycle”, or “carbocyclo”, alone or in combination with any other term, refers to a monocyclic or polycyclic non-aromatic hydrocarbon ring radical having three to twenty carbon atoms, preferably from three to twelve carbon atoms, and more preferably from three to ten carbon atoms. If polycyclic, each ring in a carbocyclyl radical is non-aromatic unless otherwise indicated. A carbocylyl radical is either completely saturated or contains one or more units of unsaturation but is not aromatic. The unsaturation, if present, may occur in any point in the ring that may result in any chemically stable configuration.

The term “cycloalkyl”, “carbocyclyl”, “carbocyclic”, “carbocycle”, or “carbocyclo” also includes hydrocarbon rings that are fused to one or more aromatic rings, such as in tetrahydronaphthyl, where the radical or point of attachment is on the non-aromatic ring.

Unless otherwise indicated, the term “cycloalkyl”, “carbocyclyl”, “carbocyclic”, “carbocycle”, or “carbocyclo” also includes each possible positional isomer of a non-aromatic hydrocarbon radical, such as in 1-decahydronaphthyl, 2- decahydronaphthyl, 1-tetrahydronaphthyl and 2-tetrahydronaphthyl. Examples of suitable cycloalkyl groups include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclohexenyl, decahydronaphthyl, tetrahydronaphthyl and the like.

The term “halogen” refers fluorine (F), chlorine (Cl), bromine (Br), or iodine (I).

The term “aryl”, alone or in combination with any other term, refers to an aromatic monocyclic or polycyclic hydrocarbon ring radical containing five to twenty carbon atoms, preferably from six to fourteen carbon atoms, and more preferably from six to ten carbon atoms. Also included within the scope of the term “aryl”, as it is used herein, is a group in which an aromatic hydrocarbon ring is fused to one or more non-aromatic carbocyclic or heteroatom-containing rings, such as in an indanyl, phenanthridinyl or tetrahydronaphthyl, where the radical or point of attachment is on the aromatic hydrocarbon ring.

Unless otherwise indicated, the term “aryl” also includes each possible positional isomer of an aromatic hydrocarbon radical, such as in 1-naphthyl, 2-naphthyl, 5-tetrahydronaphthyl, 6-tetrahydronaphthyl, 1-phenanthridinyl, 2-phenanthridinyl, 3-phenanthridinyl, 4-phenanthridinyl, 7-phenanthridinyl, 8-phenanthridinyl, 9-phenanthridinyl and 10-phenanthridinyl. Examples of aryl radicals include, but are not limited to, phenyl, naphthyl, indenyl, azulenyl, fluorenyl, anthracenyl, phenanthrenyl, tetrahydronaphthyl, indanyl, phenanthridinyl and the like. The term “aralkyl” refers to an alkyl group substituted by an aryl. Examples of aralkyl groups include, but are not limited to, benzyl and phenethyl.

The term “heterocycle”, “heterocyclic”, or “heterocyclyl”, alone or in combination with any other term, refers to a non-aromatic monocyclic or polycyclic ring radical containing three to twenty carbon atoms, preferably three to seven carbon atoms if monocyclic and eight to eleven carbon atoms if bicyclic, and in which one or more ring carbons, preferably one to four, are each replaced by a heteroatom such as N, O, and S. If polycyclic, each ring in a heterocyclyl radical is non-aromatic unless otherwise indicated. A heterocyclic ring may be fully saturated or may contain one or more units of unsaturation but is not aromatic. The unsaturation, if present, may occur in any point in the ring that may result in any chemically stable configuration. The heterocyclic ring may be attached at a carbon or heteroatom that results in the creation of a stable structure. Preferred heterocycles include 5-7 membered monocyclic heterocycles and 8-10 membered bicyclic heterocycles.

Also included within the scope of the term “heterocycle”, “heterocyclic”, or “heterocyclyl” is a group in which a non-aromatic heteroatom-containing ring is fused to one or more aromatic rings, such as in an indolinyl, chromanyl, phenanthridinyl or tetrahydro-quinolinyl, where the radical or point of attachment is on the non-aromatic heteroatom-containing ring. Unless otherwise indicated, the term “heterocycle”, “heterocyclic”, or “heterocyclyl” also includes each possible positional isomer of a heterocyclic radical, such as in 1-decahydroquinoline, 2-decahydroquinoline, 3-decahydroquinoline, 4-decahydroquinoline, 5-decahydroquinoline, 6-decahydroquinoline, 7-decahydroquinoline, 7-decahydroquinoline, 8-decahydroquinoline, 4a-decahydroquinoline, 8a-decahydroquinoline, 1-indolinyl, 2-indolinyl, 3-indolinyl, 1-tetrahydroquinoline, 2-tetrahydro-quinoline, 3-tetrahydroquinoline and 4-tetrahydro-quinoline. The term “heterocyclylalkyl” refers to an alkyl group substituted by a heterocyclyl.

Examples of heterocyclic groups include, but are not limited to, imidazolinyl, 2,3-dihydro-1H-imidazolyl, imidazolidinyl, indazolinolyl, perhydropyridazyl, pyrrolinyl, pyrrolidinyl, 4H-pyrazolyl, piperidinyl, pyranyl, pyrazolinyl, piperazinyl, morpholinyl, thiamorpholinyl, thiazolidinyl,

thiamorpholinyl, oxopiperidinyl, oxopyrrolidinyl, azepinyl, tetrahydrofuranyl, oxoazepinyl, tetrahydropyranyl, thiazolyl, dioxolyl, dioxinyl, oxathiolyl, benzodioxolyl, dithiolyl, dithiolanyl, tetrahydrothiophenyl, sulfolanyl, dioxanyl, dioxolanyl, tetahydrofurodihydrofuranyl, dihydropyranyl, tetrahydropyranodihydrofuranyl, tetradyrofurofuranyl, tetrahydropyranofuranyl, diazolonyl, phthalimidinyl, benzoxanyl, benzopyrrolidinyl, benzopiperidinyl, benzoxolanyl, benzothiolanyl and benzothianyl.

The term “heteroaryl”, alone or in combination with any other term, refers to an aromatic monocyclic or polycyclic ring radical containing five to twenty carbon atoms, preferably five to ten carbon atoms, in which one or more ring carbons, preferably one to four, are each replaced by a heteroatom such as N, O, S and P. Preferred heteroaryl groups include 5-6 membered monocyclic heteroaryls and 8-10 membered bicyclic heteroaryls.

Also included within the scope of the term “heteroaryl” is a group in which a heteroaromatic ring is fused to one or more aromatic or non-aromatic rings where the radical or point of attachment is on the heteroaromatic ring. Examples include, but are not limited to, pyrido[3,4-d]pyrimidinyl, 7,8-dihydro-pyrido[3,4-d]pyrimidine and 5,6,7,8-tetrahydro-pyrido[3,4-d]pyrimidine. Unless otherwise indicated, the term “heteroaryl” also includes each possible positional isomer of a heteroaryl radical, such as in 2-pyrido[3,4-d]pyrimidinyl and 4-pyrido[3,4-d]pyrimidinyl. The term “heteroaralkyl” refers to an alkyl group substituted by a heteroaryl.

Examples of heteroaryl groups include, but are not limited to, imidazolyl, quinolyl, isoquinolyl, indolyl, indazolyl, pyridazyl, pyridyl, pyrrolyl, pyrazolyl, pyrazinyl, quinoxalyl, pyrimidinyl, pyridazinyl, furyl, thienyl, triazolyl, thiazolyl, carbazolyl, carbolinyl, tetrazolyl, benzofuranyl, oxazolyl, benzoxazolyl, isoxozolyl, isothiazolyl, thiadiazolyl, furazanyl, oxadiazolyl, benzimidazolyl, benzothienyl, quinolinyl, benzotriazolyl, benzothiazolyl, isoquinolinyl, isoindolyl, acridinyl and benzoisoxazolyl.

The term “heteroatom” means nitrogen, oxygen, sulfur, or phosphorus and includes any oxidized form of nitrogen, such as N(O) $[N^{+}-O^{-}]$, sulfur such as S(O) and $S(O)_2$, phosphorus such as PO_3 and PO_4 and the quaternized

form of any basic nitrogen. Suitable substituents on a substitutable ring nitrogen include alkyl, $-N(R')_2$, -C(O)R', $-CO_2R'$, -C(O)C(O)R', $-C(O)CH_2C(O)R'$, $-SO_2R'$, $-SO_2N(R')_2$, $-C(=S)N(R')_2$, $-C(=NH)-N(R')_2$, and $-NR'SO_2R'$; wherein R' is hydrogen, alkyl, phenyl (Ph), -OPh, $-CH_2Ph$, wherein said alkyl or phenyl is optionally substituted by one or more groups independently chosen from alkyl, amino, alkylamino, dialkylamino, aminocarbonyl, halo, alkylaminocarbonyl, dialkylaminocarbonyl, alkylaminocarbonyloxy, dialkylaminocarbonyloxy, alkoxy, nitro, cyano, carboxy, alkoxycarbonyl, alkylcarbonyl, hydroxy, haloalkoxy, and haloalkyl.

The term "alkylene chain" refers to a straight or branched hydrocarbon chain that may be fully saturated or have one or more units of unsaturation. The unsaturation may occur in any stable point along the chain. The double bond(s) in the unsaturated alkylidene chain may be in either the cis or trans configuration.

A combination of substituents or variables is permissible only if such a combination results in a stable or chemically feasible compound. A stable compound or chemically feasible compound is one in which the chemical structure is not substantially altered when kept at a temperature of 40 °C or less, in the absence of moisture or other chemically reactive conditions, for at least a week.

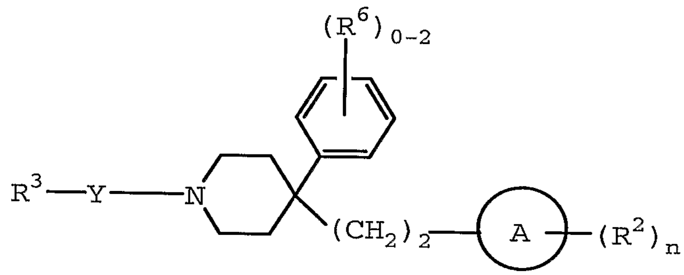
Unless otherwise stated, structures depicted herein are also meant to include all endo or exo, cis or trans isomers as well as all stereochemical forms of the structure, i.e., the R and S configurations for each asymmetric center. Therefore, racemates and racemic mixtures, single enantiomers, diastereomeric mixtures and individual diastereoisomers of the present compounds are expressly included within the scope of the invention. Although the specific compounds exemplified herein may be depicted in a particular stereochemical configuration, compounds having either the opposite stereochemistry at any given chiral center or mixtures thereof are also envisioned.

Unless otherwise stated, structures depicted herein are also meant to include compounds which differ only in the presence of one or more

isotopically enriched atoms. For example, compounds having the present structures except for the replacement of a hydrogen by a deuterium or tritium, or the replacement of a carbon by a ^{13}C- or ^{14}C-enriched carbon are also within the scope of this invention.

It will be apparent to one skilled in the art that certain compounds of this invention may exist in alternative tautomeric forms. All such tautomeric forms of the present compounds are within the scope of the invention. Unless otherwise indicated, the representation of either tautomer is meant to include the other.

Certain preferred compounds of the present invention are those represented by formula II:



(II)

or a pharmaceutically acceptable derivative thereof, wherein R^2, R^3, R^6, n, Y and Ring A are as defined for formula I.

Preferred compounds of formula II are those wherein Ring A is a heterocycle having one ring nitrogen and 0-1 additional ring oxygen or ring nitrogen. Other preferred compounds of formula II are those wherein Ring A is piperidinyl, piperaziny, pyrrolidinyl, azabicyclo[3.2.1] octanyl, aza-bicyclo[3.2.1]octenyl or oxa-aza-bicyclo [4.3.1]decanyl. In some embodiments of the invention, Ring A is connected to the alkylene chain X through an endocyclic nitrogen.

Also preferred are compounds of formula II, wherein R^2 is aryl, aralkyl, heteroaryl, heterocyclyl, -N(H)(-V_m-R^+), or -N(alkyl)(-V_m-R^+), wherein V is -C(O)-, -S(O)$_2$-, -C(O)O- or -C(O)-N(H)-, m is 0 or 1, R^+ is phenyl or benzyl, and said aryl, aralkyl, heteroaryl or heterocyclyl is optionally substituted. More preferably, R^2 of compounds of formula II is phenyl, naphthyl, benzyl, -NH-phenyl, -NH-benzyl, -NHC(O)-phenyl, -NHSO$_2$-phenyl,

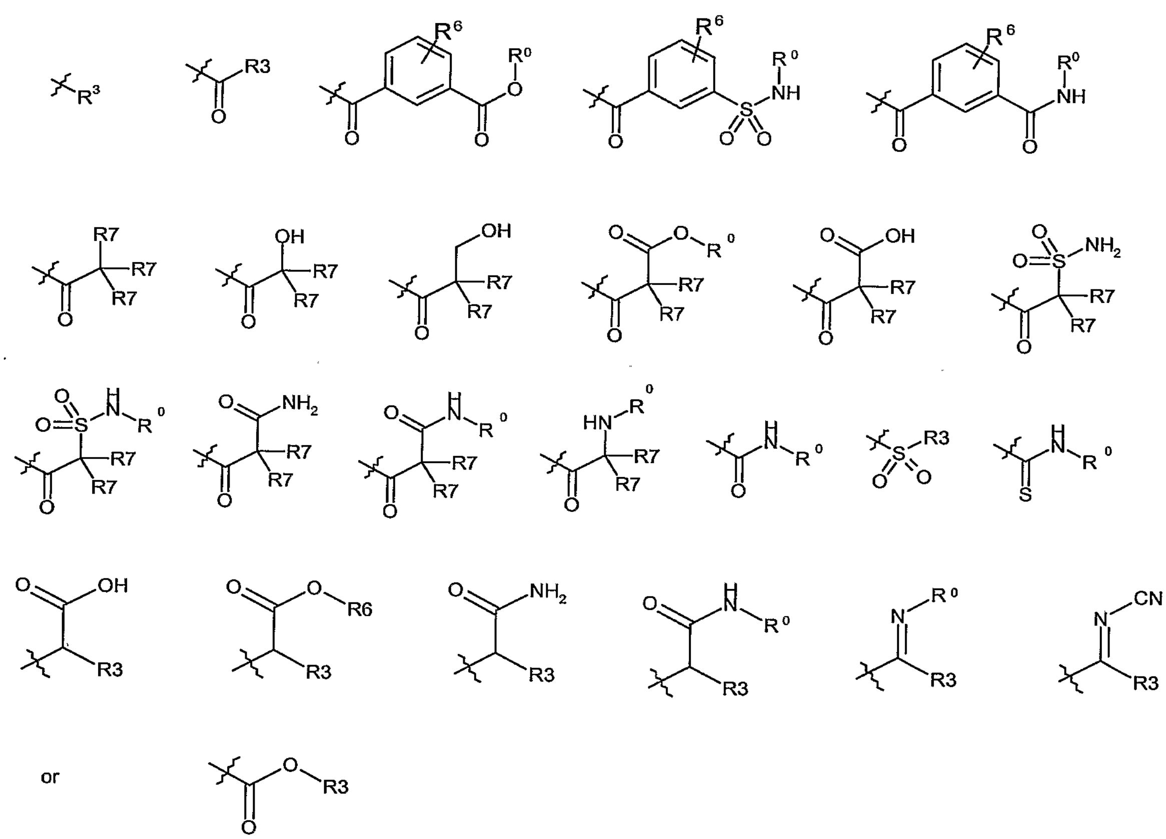
-NHC(O)NH-phenyl, benzoimidazolyl, dihydrobenzo-imidazolyl, oxodihydrobenzoimidazolyl, 3H-indolyl, quinolinyl, dihydro-1H-isoindolyl, dioxodihydro-1H-isoindolyl, tetrahydroquinoxalinyl, dioxotetrahydro-quinoxalinyl, 3H-imidazo[4,5-b]pyridinyl, dihydro-1H-imidazo [4,5-b]pyridinyl, benzotriazolyl, oxadiazolyl or triazolyl, wherein each member of R^2 is optionally substituted. Preferred substituents of R^2 include alkyl, halo, $-SO_2R^0$, $-CF_3$, alkoxy, $-NR^0$, $-N(R^0)C(O)R^0$, $-N(R^0)C(O)OR^0$, $-N(R^0)C(S)N(R^0)_2$, =O, $-(CH_2)_{1-6}-C(O)R^0$, optionally substituted alkyl, and optionally substituted aralkyl. More preferred substituents of R^2 include methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, t-butyl, F, Cl, $-SO_2CH_3$, $-CF_3$, -OMe, -OEt, $-NH_2$, -NHMe, -N(H)C(O)Me, -N(H)C(O)OMe, -N(H)C(O)OEt, -N(H)C(S)N(H)(Me), =O, $-(CH_2)_2SO_2Ph$, =O, $-CH_2$-C(O)-cyclopropyl, and methoxy substituted benzyl. Preferably, n is 1-3, and more preferably, n is 1-2. In certain embodiments of the invention, R^2 is attached to Ring A through a R^2 nitrogen.

Preferred Y of formula II includes -C(O)-, -O-C(O)-, $-N(R^0)-C(O)-$, $-S(O)_2-$, -O-C(=N-CN)-, -S-C(=N-CN)-, $-N(R^0)-C(=N-CN)-$, -C(=N-CN)-, $-N(R^0)-C(S)-$, $-N(R^0)-C(=N-OR^0)-$, $-N(R^0)-C[=N-S(O)_t-R^0]$, $-O-C(=N-R^0)-$, $-N(R^0)-C[=N-C(O)-R^0]$, $-N(R^0)-C(=N-R^0)-$, and $-C(=N-R^0)-$. More preferably, each R^o in Y is independently R* and m is 1.

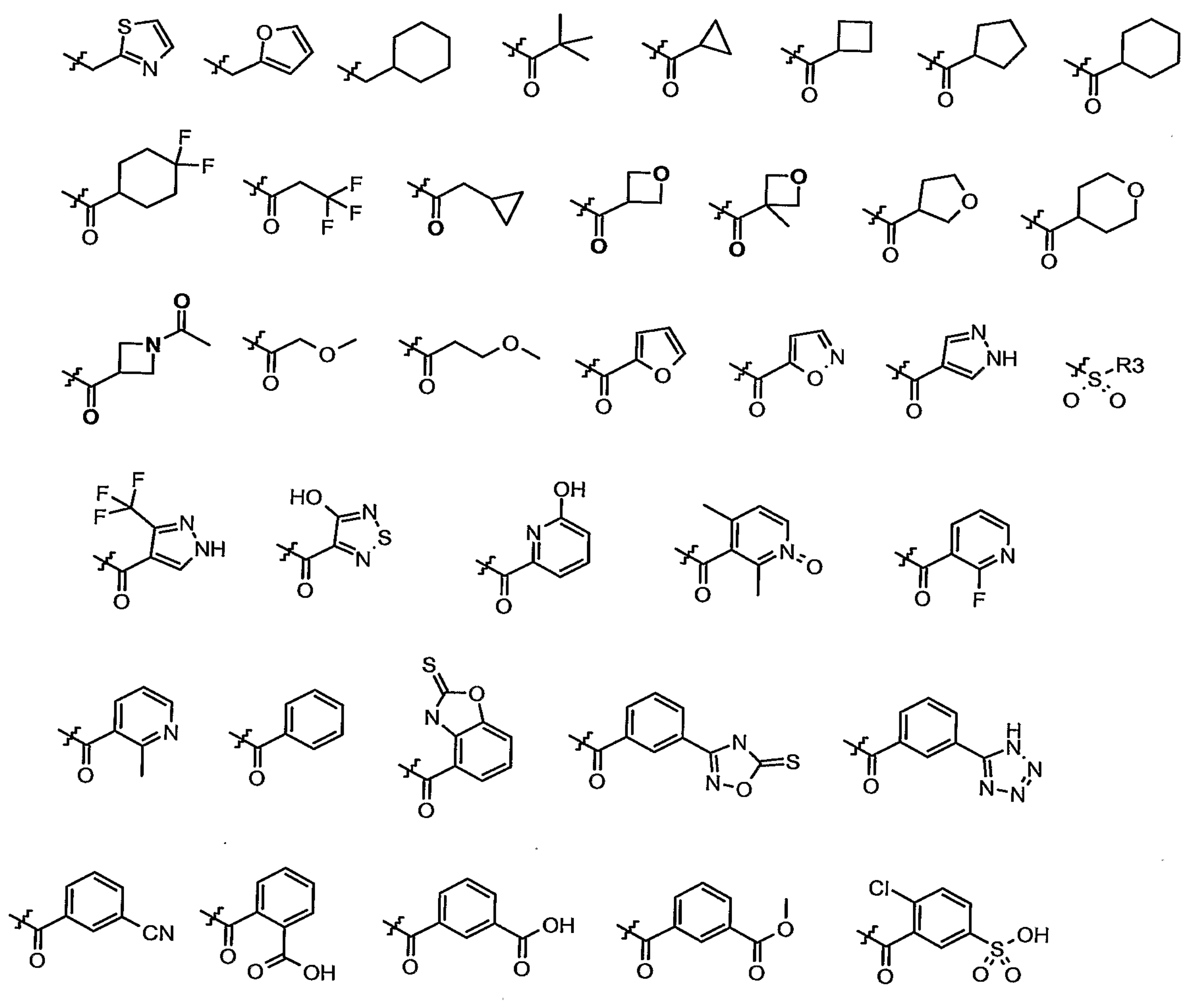
Preferred R^3 of formula II includes optionally substituted alkyl, aryl, heteroaryl, heterocyclyl and carbocyclyl. More preferred R^3 of formula II includes optionally substituted fully saturated alkyl, 3-7 membered carbocyclyl, 5-7 membered aryl, 6-10 membered heteroaryl and 4-10 membered heterocyclyl. Even more preferred R^3 of formula II includes cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclohexenyl, tetrahydrofuranyl, azetidinyl, piperidinyl, hexahydrofuro[2,3-b]furanyl, oxopyrrolidinyl, dihydro-2H-[1,3]thiazinyl, tetrahydro-pyrimidinyl, dihydrobenzo[1,4]dioxinyl, dihydro-2H-benzo[1,2,4]thiadiazinyl, dihydrobenzo[d]isothiazolyl, morpholinyl, dihydro-1H-imidazolyl, dihydrobenzooxazolyl, chromenyl, dihydroquinolinyl, pyrrolyl, benzotriazolyl, benzothiazolyl, benzofuranyl, furanyl, pyridyl, thienyl, thiadiazolyl, isoxazolyl,

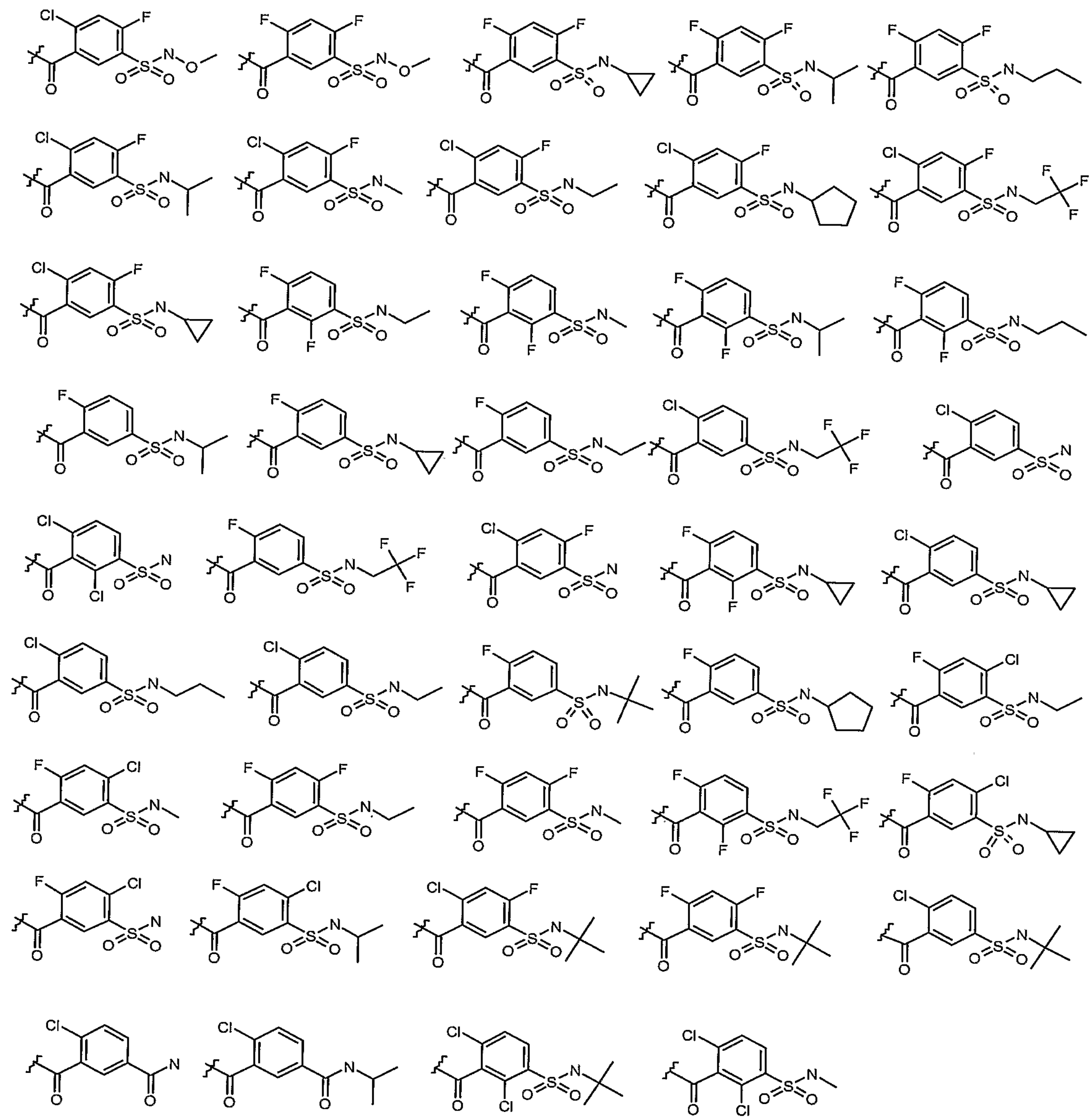
triazolyl, thiazolyl, benzoyl, isothiazolyl, imidazolyl, indolyl, pyrazolo[3,4-b]pyridinyl, quinoxalinyl, and phenyl. Preferred substituents of R^3 includes halo, methylenedioxy, $-OR^0$, R^0, $-C(O)OR^0$, $-SO_2R^0$, $-SO_2(OR^0)$, $-SO_2N(R^0)_2$, $-SO_2N(R^0)OR^0$, and $-SO_2N(R^0)C(O)R^0$. More preferred substituents of R^3 includes Cl, Br, F, CF_3, Me, tetrazolyl, methylenedioxy, -OMe, -C(O)OH, $-SO_2R^0$, $-SO_2(OH)$, $-SO_2NH_2$, $-SO_2NHMe$, $-SO_2N(H)C(O)Me$, and $-SO_2N(H)OMe$.

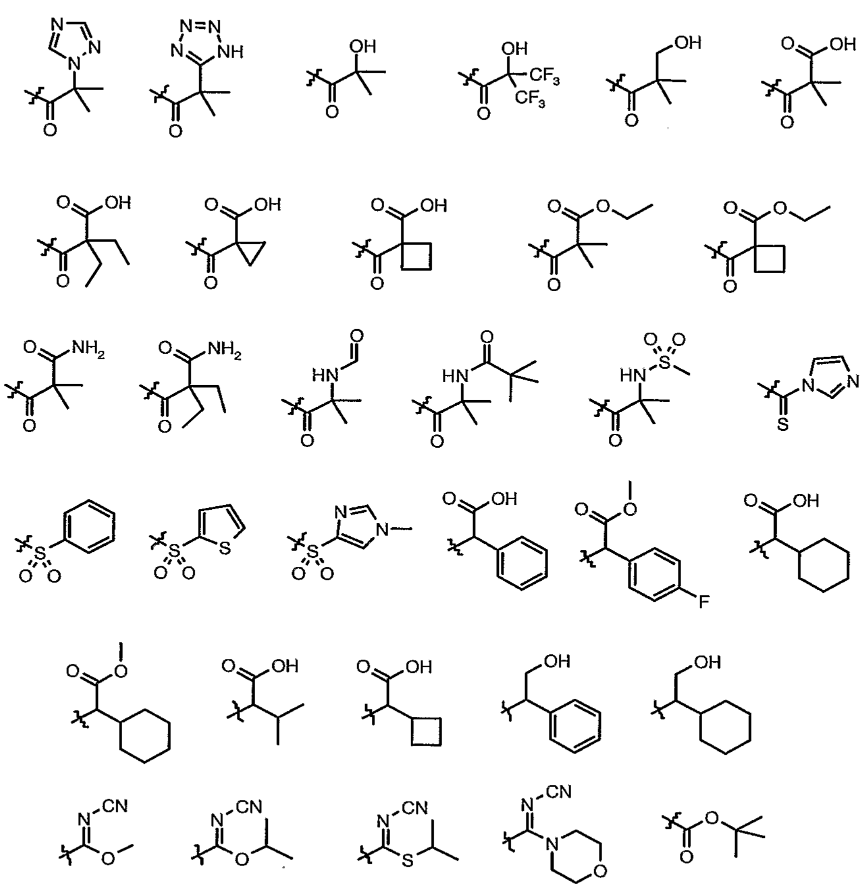
In certain embodiments of the invention, $-(Y)_m-R^3$ is selected from the following:

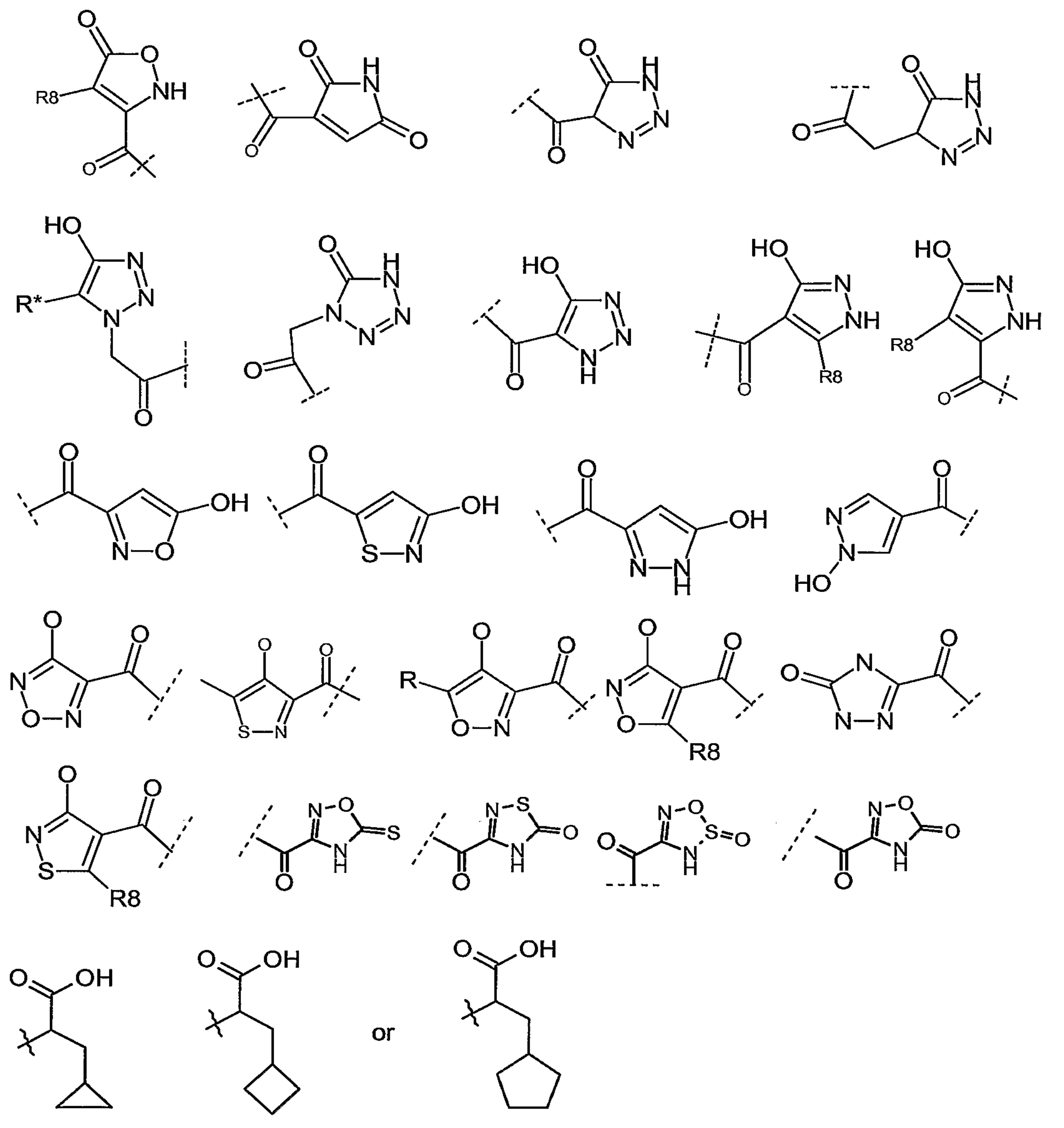


More preferably, $-(Y)_m-R^3$ is selected from the following:









In one embodiment m is 1, Y is –C(O)-, and R^3 is aryl, heteroaryl, alkyl, or cycloalkyl, each optionally substituted.

In one embodiment m is 1, Y is –(C=N-CN)-O-, and R^3 is optionally substituted aryl, optionally substituted alkyl, optionally substituted cycloalkyl, optionally substituted heteroaryl, or optionally substituted heterocyclyl.

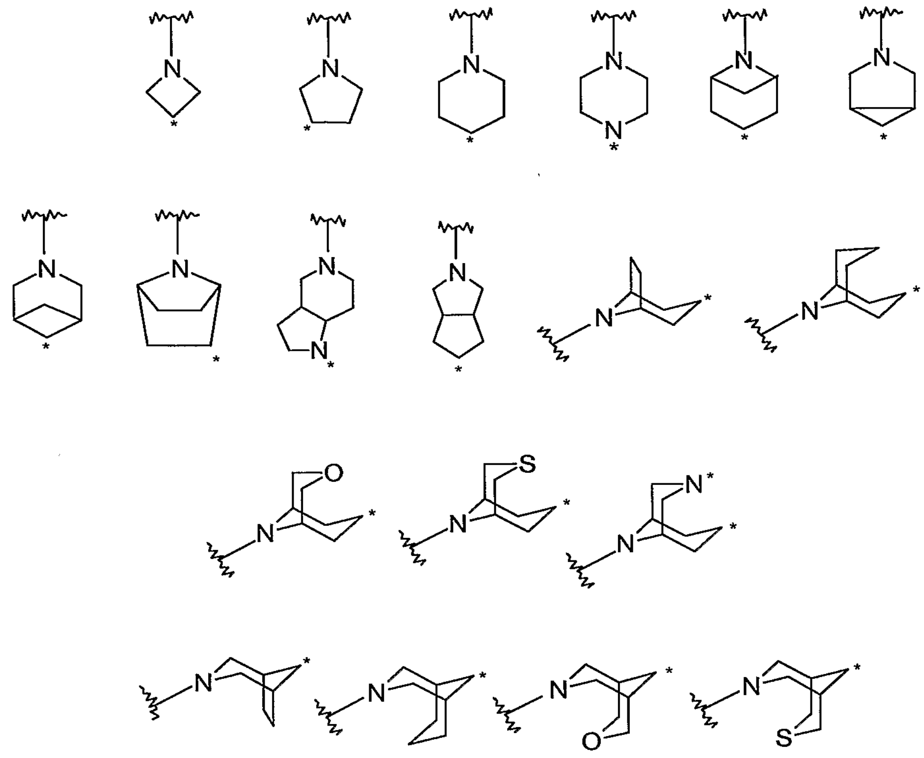
In one embodiment m is 1, Y is $-(CH_2)$-, and R^3 is optionally substituted aryl.

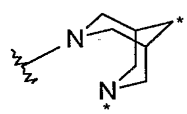
In one embodiment m is 1, Y is –C(O)O-, and R^3 is optionally substituted alkyl or optionally substituted aryl.

In one embodiment m is 0 and R^3 is optionally substituted heteroaryl or optionally substituted heterocyclyl.

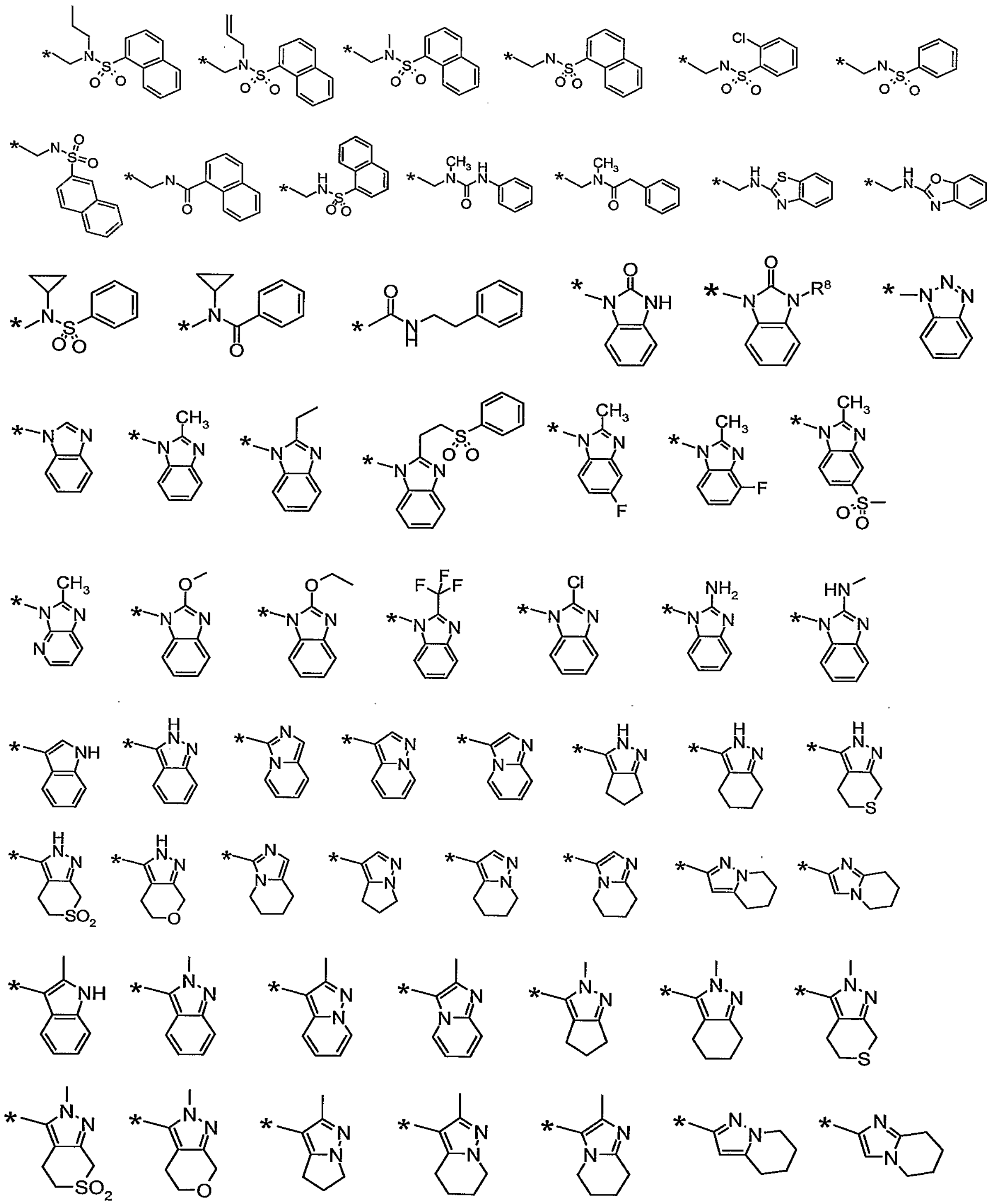
In one embodiment X is $-(CH_2)$-, $-(CH_2\text{-}CH_2)$-, or $-(CH_2\text{-}CH_2\text{-}CH_2)$-. Further X is optionally substituted by one or more halogen or oxo. Still further X is disubstituted with halogen. Still further X is disubstituted with fluoro. Specifically X may be $-(CF_2\text{-}CH_2)$-. Further X optionally has 1-3 heteroatoms selected from oxygen, phosphorus, sulfur, or nitrogen.

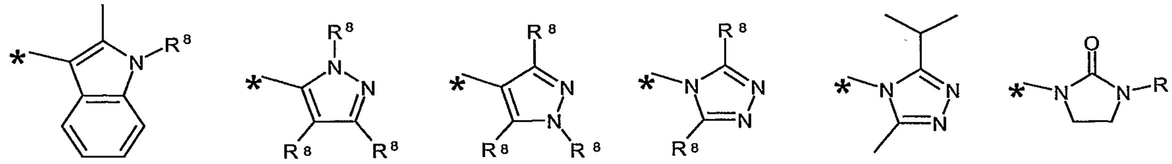
In one embodiment the A ring is selected from the following, where the asterisk (*) indicates the preferred, but not limiting, point(s) of substitution:

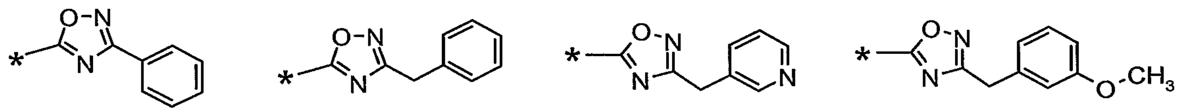


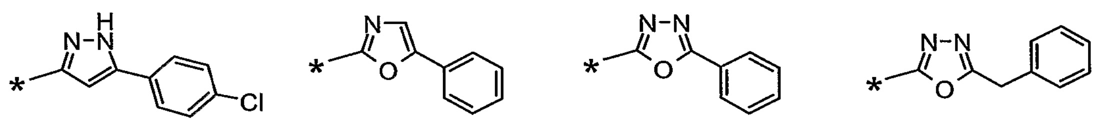
or 

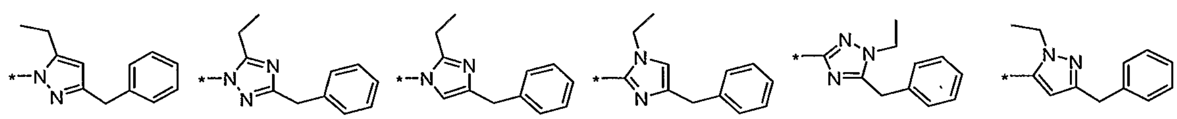
Suitably each R^2, with the asterisk (*) indicating a preferred, but not limiting, point of substitution from Ring A, independently is selected from

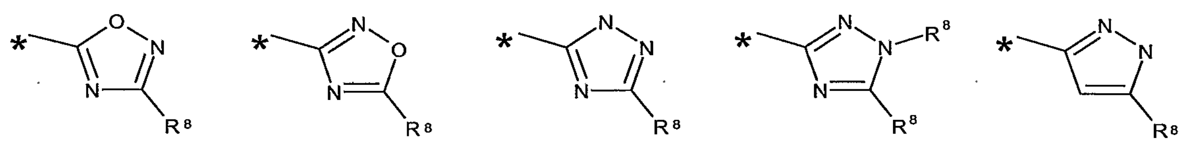


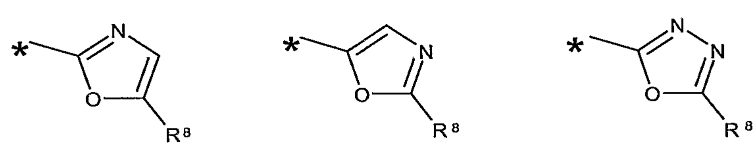


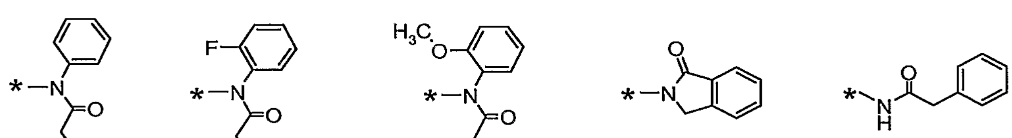


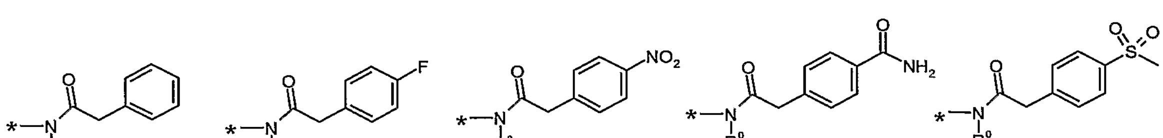


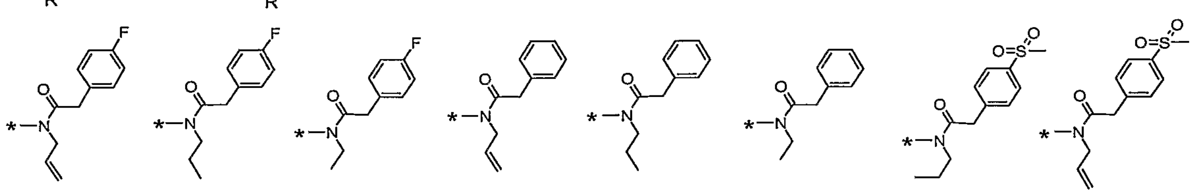


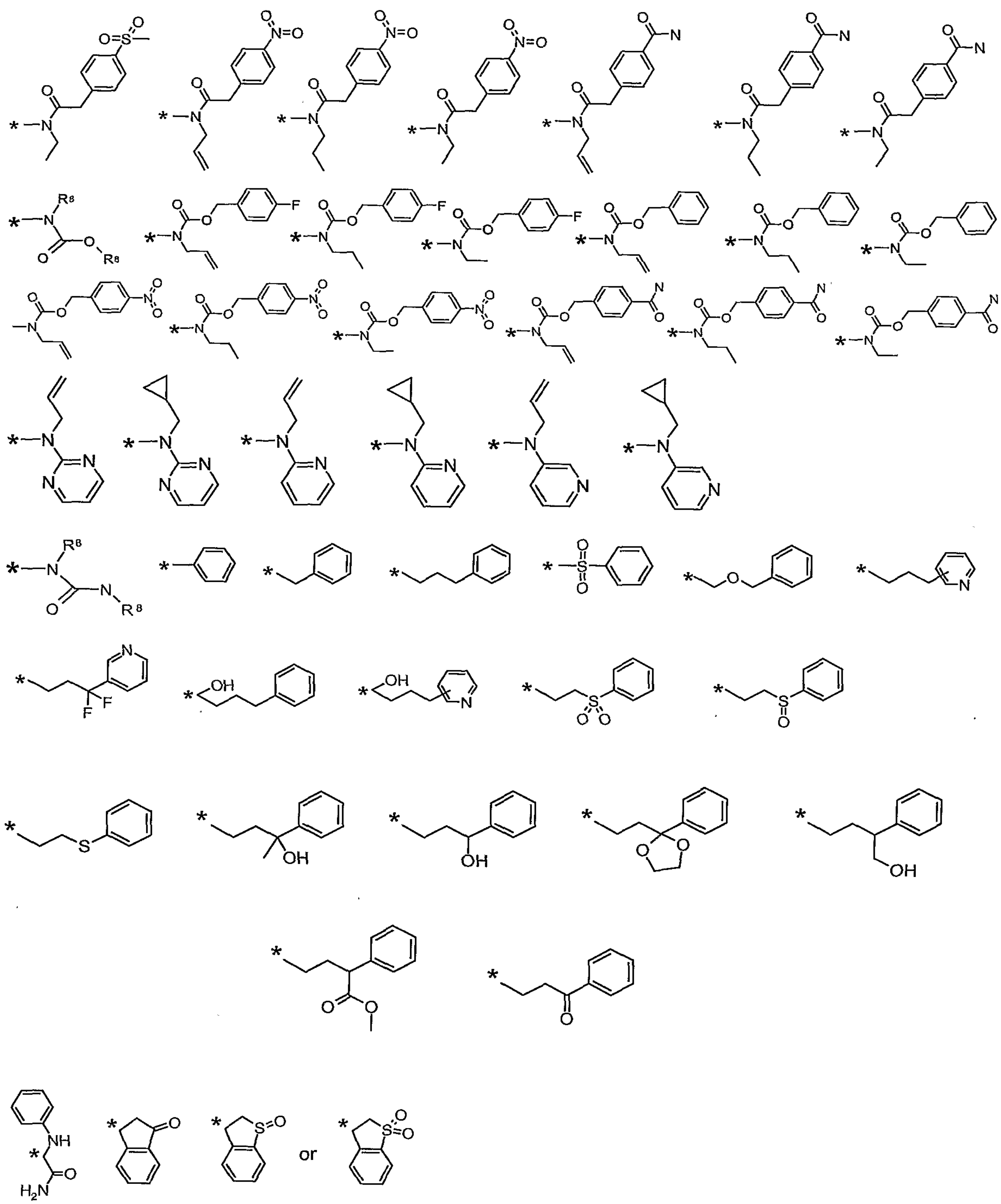




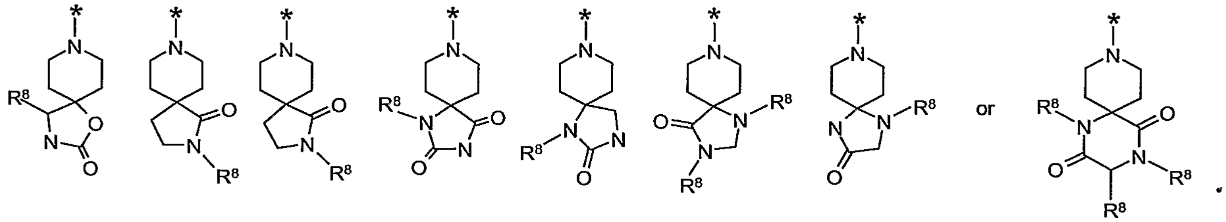




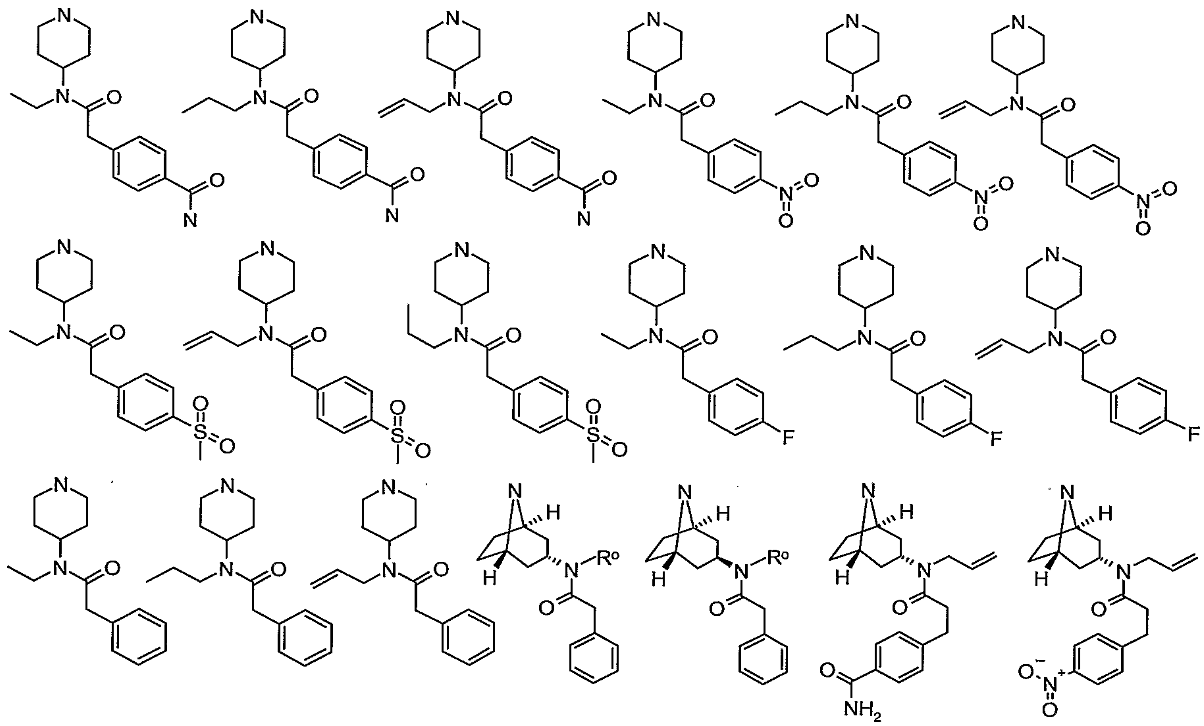


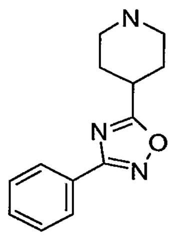
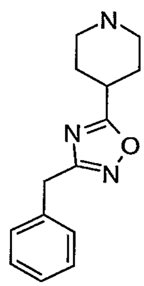
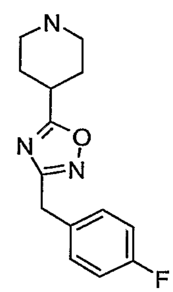
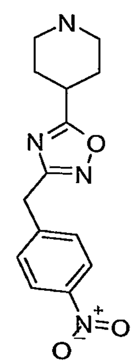
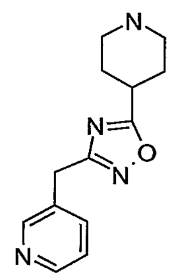
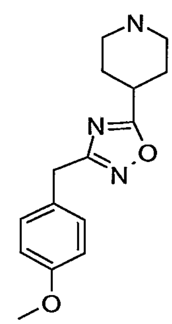


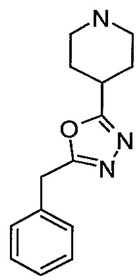
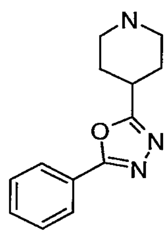
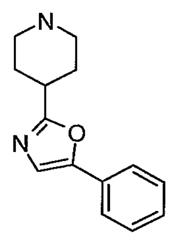
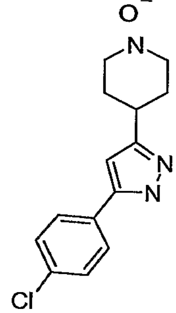
In one embodiment the ring A, with two geminal R^2s, is selected from:

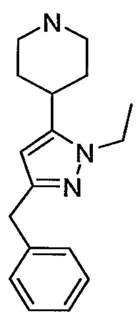
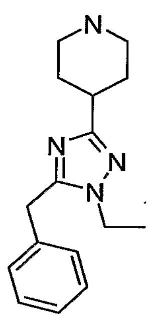
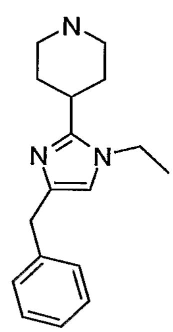
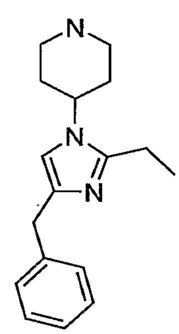
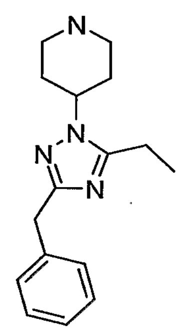
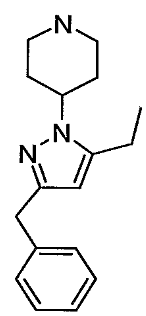


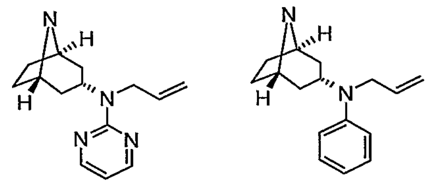
Suitably the A ring is tropane or piperidine, either optionally substituted with one or more R^2. Preferrably, A--R^2 is comprised of one of the following:

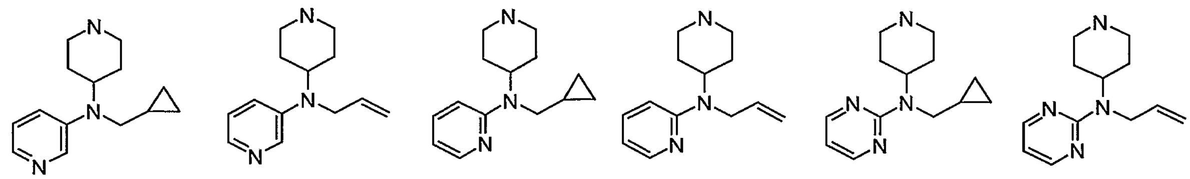


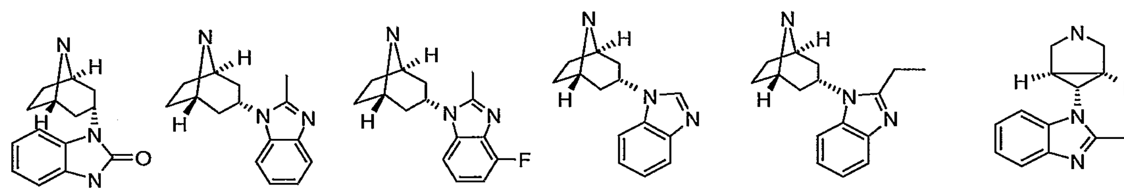







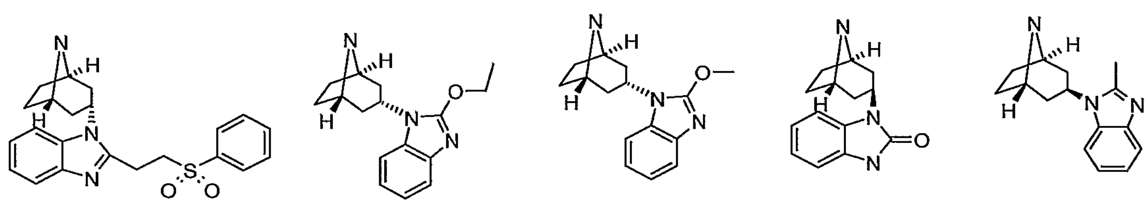





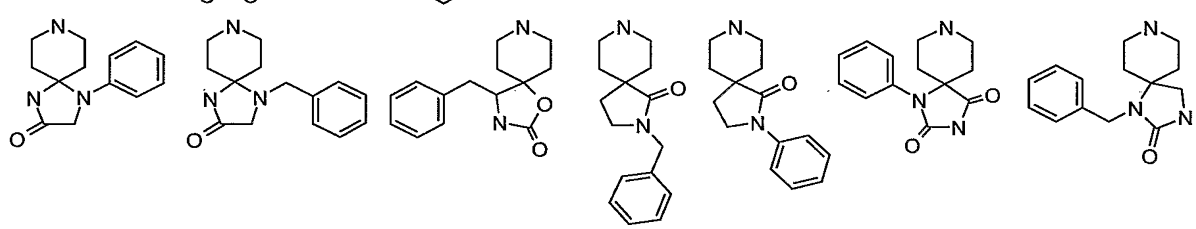







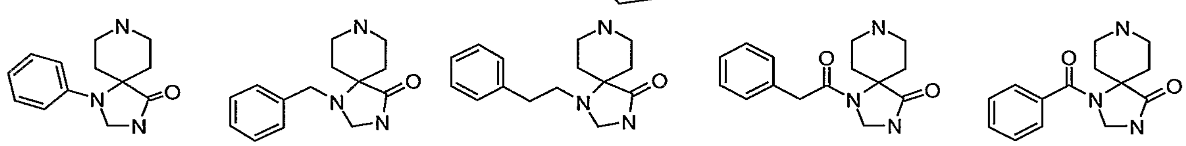


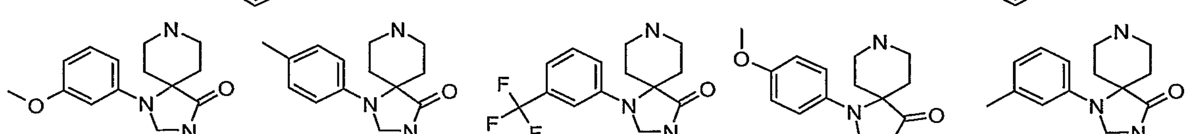


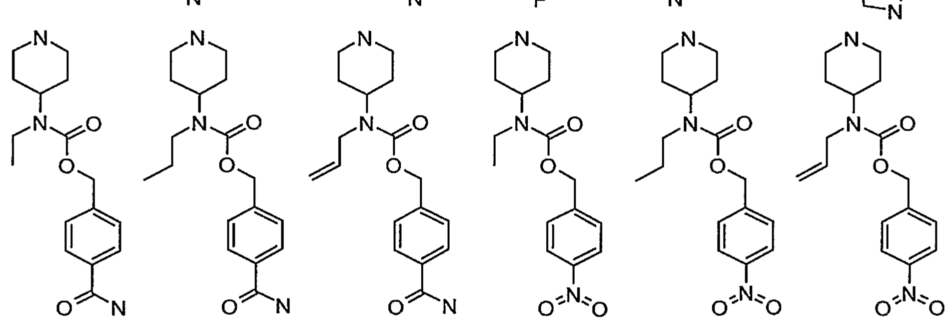


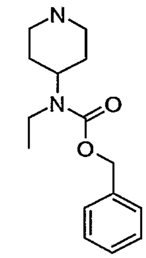
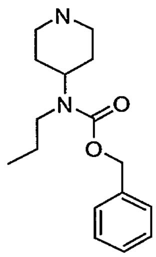
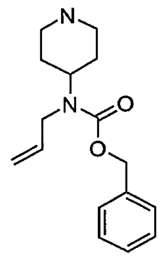
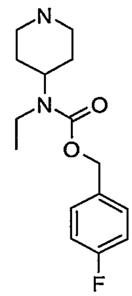
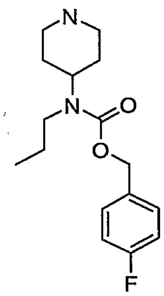
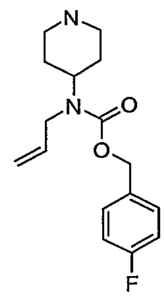


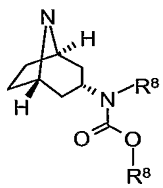
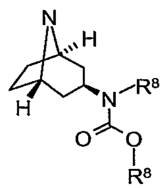
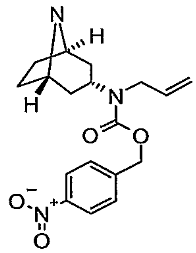


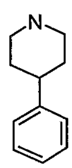
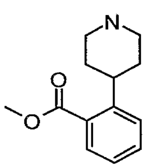
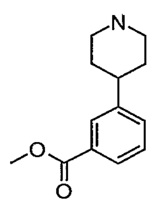
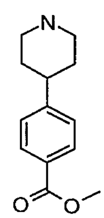
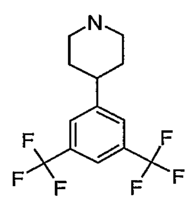
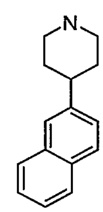
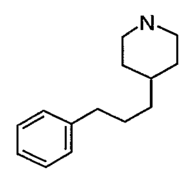


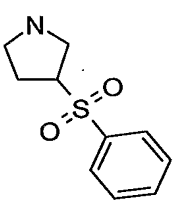
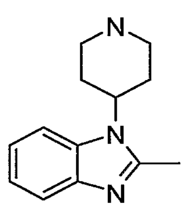
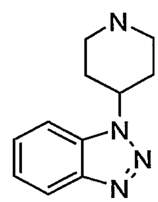
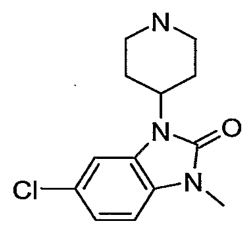
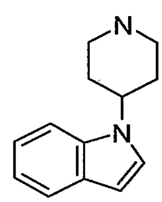


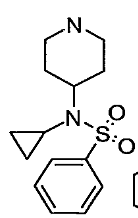
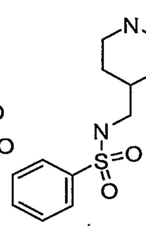
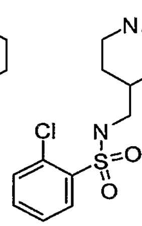
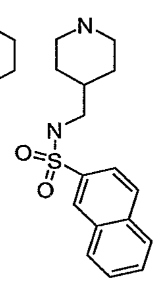
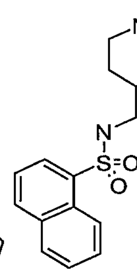
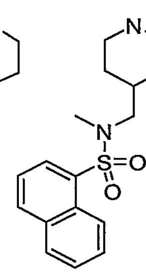
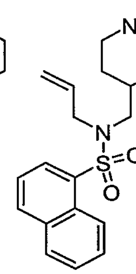
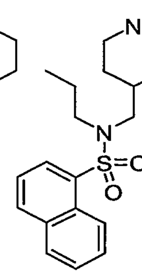


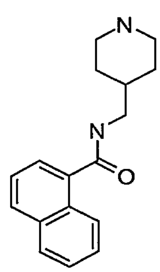
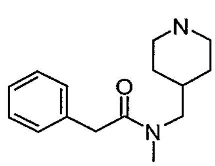
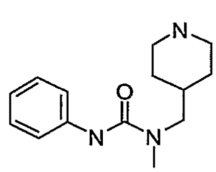
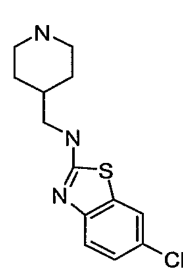







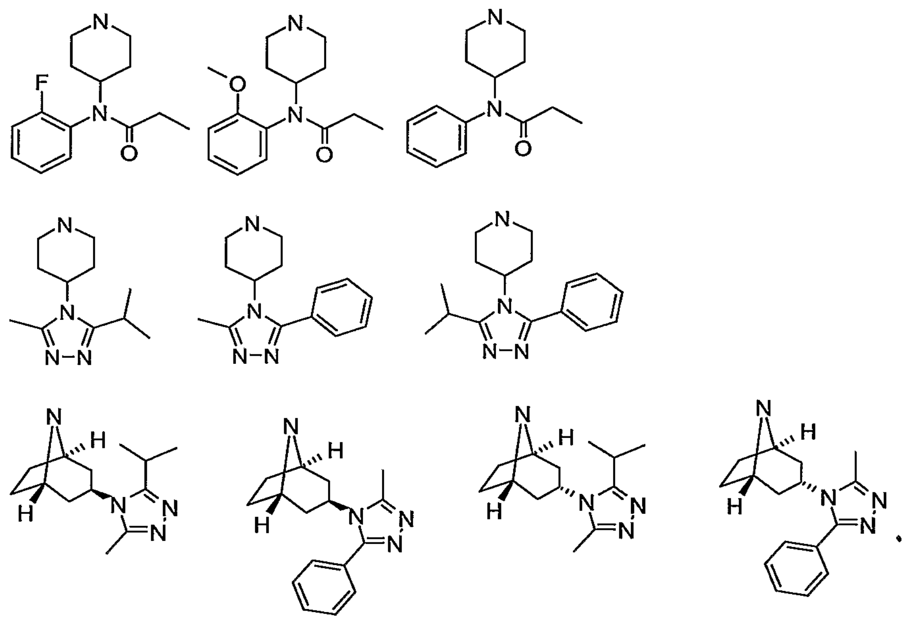




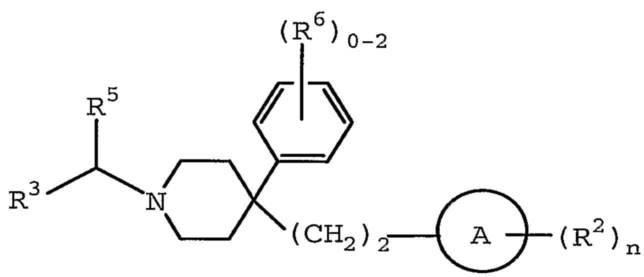







In one embodiment the A ring contains at least one additional nitrogen atom and said A ring optionally is N-substituted. Suitably the A ring is N-substituted with $–(CH_2)_a$-(V_b-R+).

Preferred R^6 of formula II includes alkyl, halo, SO_2R^0 and $SO_2N(R^0)_2$. More preferred R^6 of formula II includes Me, F, Cl, SO_2NH_2, SO_2Me, and methylenedioxy.

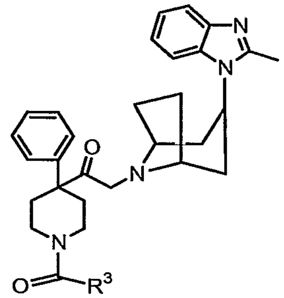
Other preferred compounds of the present invention are those represented by formula III:



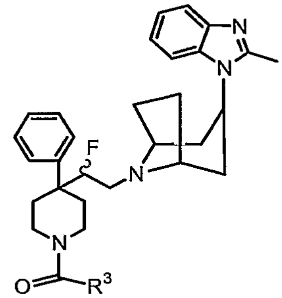
(III)

or a pharmaceutically acceptable derivative thereof, wherein R^2, R^3, R^5, R^6, n and Ring A are as defined for formula I. Preferred compounds of formula III are those wherein R^3 is optionally substituted aryl. More preferably, R^3 is phenyl optionally substituted by one or more alkyl (such as Me) or halo (such as F and Cl).

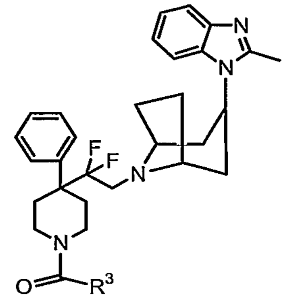
Other preferred compounds of the present invention are those represented by formulae IV-IX:



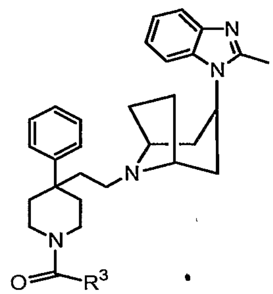
IV



V



VI



VII

R^3 in formulae IV-VII is as defined for formula I.

Preferred compounds of formula I have one or more, and more preferably all, of the features selected from the group consisting of:

(a) R^1 is alkyl, aryl, heteroaryl or heterocyclyl, wherein said alkyl is optionally substituted by one or more R^7, said aryl or heteroaryl is optionally substituted by one or more R^6, and said heterocyclyl is optionally substituted by one or more R^8;

(b) X is a C_{1-5} alkylene chain optionally substituted by one or more groups chosen from =O and halo;

(c) Ring A is an 8-10 membered bicyclic ring having 0-5 ring heteroatoms chosen from oxygen, sulfur and nitrogen;

(d) R^2 is aryl, heteroaryl or heterocyclyl, wherein said aryl or heteroaryl is optionally substituted by one or more R^6 and said heterocyclyl is optionally substitued by one or more R^8;

(e) Y is -C(R^{o})[C(O)OR^{o}]-, -C(O)-, -O-C(O)-, -N(R^0)-C(O)-, -S(O)$_2$-, -O-C(=N-CN)-, -S-C(=N-CN)-, -N(R^0)-C(=N-CN)-,

-C(=N-CN)-, -N(R^0)-C(S)-, -N(R^0)-C(=N-OR^0)-, -N(R^0)-C[=N-S(O)$_t$-R^0], -O-C(=N-R^0)-, -N(R^0)-C[=N-C(O)-R^0], -N(R^0)-C(=N-R^0)-, or -C(=N-R^0)-; wherein each R^o is independently R* and m is 1; and

(f) R^3 is alkyl, aryl, heteroaryl, heterocyclyl or carbocyclyl, wherein said alkyl is optionally substituted by one or more R^7, said aryl or heteroaryl is optionally substituted by one or more R^6, and said heterocyclyl or carbocyclyl is optionally substituted by one or more R^8.

More preferred compounds of the present invention have one or more, and more preferably all, of the features selected from the group consisting of:

(a) R^1 is aryl optionally substituted by one or more R^6;

(b) X is a C_2 alkylene chain optionally substituted by one or more groups chosen from =O and halo;

(c) Ring A is an 8-9 membered bicyclic ring having one ring nitrogen and 0-4 additional ring heteroatoms chosen from oxygen, sulfur and nitrogen;

(d) R^2 is heteroaryl optionally substituted by one or more R^6, or heterocyclyl optionally substituted by one or more R^8;

(e) Y is -C(R^0)[C(O)OR^0]-, -CH(COOH)-, -C(O)-, -O-C(O)-, -N(R^0)-C(O)-, -O-C(=N-CN)-, or -N(R^0)-C(S)-; wherein each R^o is independently R* and m is 1; and

(f) R^3 is alkyl optionally substituted by one or more R^7, aryl or heteroaryl wherein said aryl or heteroaryl is optionally substituted by one or more R^6.

Other more preferred compounds of the present invention have one or more, and more preferably all, of the features selected from the group consisting of:

(a) R^1 is phenyl optionally substituted by one or more groups chosen from alkyl, halo, -OR^0, -CF_3, R^0, -SO_2R^0, methylenedioxy and -$SO_2N(R^0)_2$; wherein each R^0 is independently R*;

(b) X is a saturated C_2 alkylene chain optionally substituted by one or more groups chosen from =O and halo;

(c) Ring A is an 8-9 membered non-aromatic bicyclic ring having one ring nitrogen and 0-1 additional ring heteroatoms chosen from oxygen, sulfur and nitrogen;

(d) R^2 is a 9-10 memebered bicyclic heteroaryl or heterocyclyl each having one to three ring nitrogens, wherein said heteroaryl is optionally substituted by one or more groups chosen from alkyl, halo, $-SO_2R^0$, $-CF_3$, alkoxy, $-NR^0$, $-N(R^0)C(O)R^0$, $-N(R^0)C(O)OR^0$, and $-N(R^0)C(S)N(R^0)_2$ and said heterocyclyl is optionally substituted by one or more groups chosen from alkyl, halo, $-SO_2R^0$, $-CF_3$, alkoxy, $-NR^0$, $-N(R^0)C(O)R^0$, $-N(R^0)C(O)OR^0$, $-N(R^0)C(S)N(R^0)_2$ and =O;

(e) Y is -CH(COOH)-, -CH(COOMe)-, -C(O)-, -O-C(O)-, $-N(R^0)$-C(O)-, -O-C(=N-CN)-, or $-N(R^0)$-C(S)-; wherein each R^0 is independently H and m is 1; and

(f) R^3 is methyl, butyl, pentyl, cyclobutyl optionally substituted by one or more R^8, phenyl, pyrazolyl, thiadiazolyl, benzotriazolyl, pyrrolyl, benzothiazolyl, benzofuranyl, furanyl, pyridyl, thienyl, isoxazolyl, triazolyl, thiazolyl, isothiazolyl, imidazolyl, indolyl, pyrazolo[3,4-b]pyridinyl, or quinoxalinyl, wherein each member of R^3 except methyl, butyl, pentyl and cyclobutyl is optionally substituted by one or more R^6 and said methyl, butyl and pentyl are optionally substituted by one or more R^7.

Even more preferred compounds of the present invention have one or more, and more preferably all, of the features selected from the group consisting of:

(a) R^1 is phenyl optionally substituted by one or more groups chosen from halo, $-CF_3$, methyleneoxy, alkyl, alkoxy and sulfonamide;

(b) X is a saturated C_2 alkylene chain;

(c) Ring A is azabicyclo[3.2.1]octanyl or piperidinyl;

(d) R^2 is benzoimidazolyl, imidazo[4,5-b]pyridinyl, benzotriazolyl, or oxadiazolyl, wherein each member of R^2 is optionally substituted by one or more groups chosen from alkyl, halo, R^0, $-SO_2R^0$, $-CF_3$, alkoxy, benzyl, $-CH_2$-pyridyl and $-NR^0$;

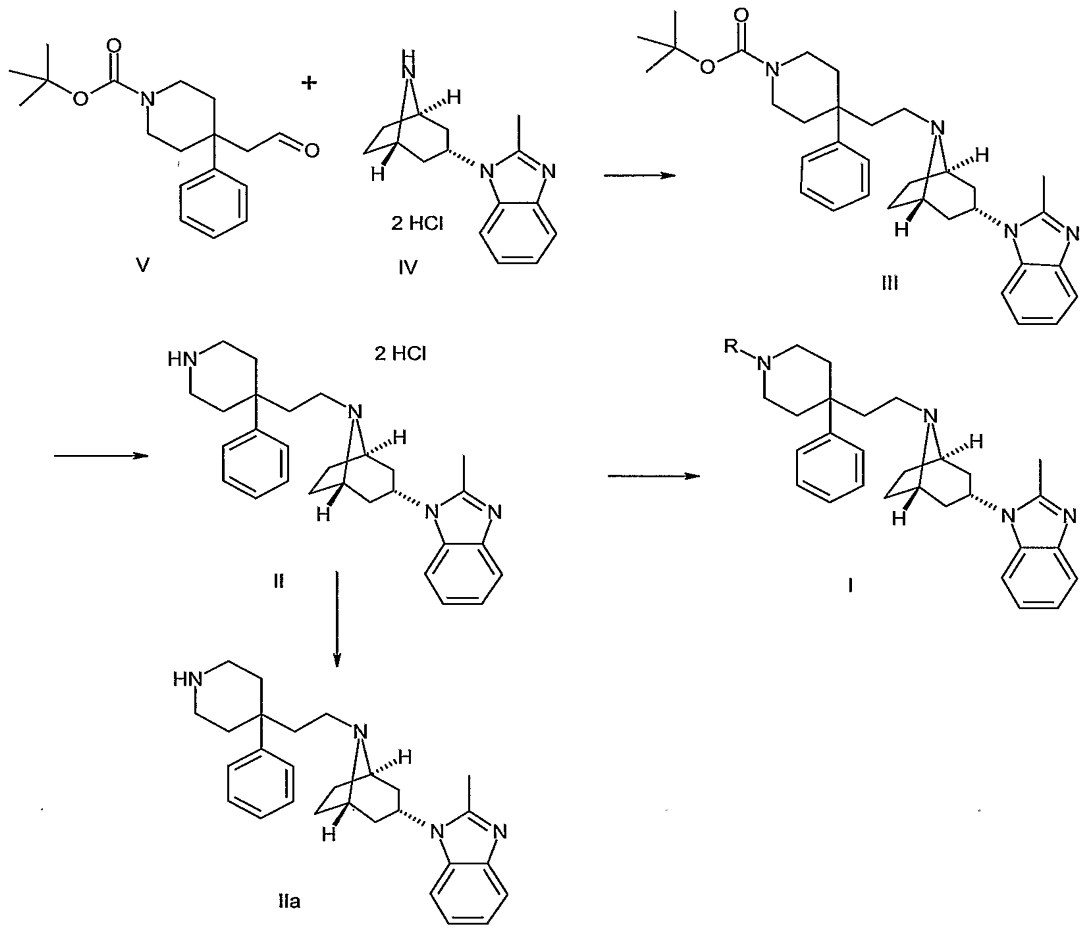
(e) Y is -C(O)-, -C(S)-, -C(O)C(O)-, -O-C(O)-, -CH(COOH)-,

-CH(COOMe)-, -NH-C(O)-, -NH-C(S)-, $-SO_2-$, $-CH_2-$, or -O-C(=N-CN)- and m is 0 or 1; and

(f) R^3 is methyl, butyl, pentyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclohexenyl, cycloheptanyl, phenyl, naphthyl, thienyl, furanyl, benzofuranyl, thiazolyl, isothiazolyl, isoxazolyl, pyrazolyl, pyrrolyl, piperidinyl, pyrimidinyl, benzooxazole-2-thionyl, imidazolyl, oxiranyl, pyrazolo[3,4-b]pyridinyl, pyrazolo[1,5-a]pyrimidinyl, thioxodihydrotriazinonyl, dihydrotetrazolethionyl, benzotriazolyl, pyrrolidinonyl, pyrrolidine-2,5-dionyl, imidazolidin-2-onyl, indolyl, dihydrofuran-2-onyl, pyrimidine-2,4-dionyl, quinolinyl, pyran-2-onyl, benzothiazolyl, dihydrobenzo[1,4]dioxinyl, quinoxalinyl, chromen-4-onyl, tetrazolyl, pyridyl, thiadiazolyl or thiazinedionyl, wherein said R^3 is optionally substituted by one or more groups chosen from $-C(O)OR^0$, $-C(O)N(R^0)SO_2R^0$, $-N(R^0)C(O)R^0$, $-N(R^0)C(O)OR^0$, NO_2, CN, CF_3, halo, methylenedioxy, $-OR^0$, $-N(R^0)_2$, R^0, tetrazolyl, $-SO_2R^0$, $-SO_2(OR^0)$, $-SO_2N(R^0)_2$, $-SO_2N(R^0)OR^0$, $-SO_2N(CH_2CH_2OR^0)_2$, $-O-SO_2N(R^0)_2$, $-NR^0SO_2R^0$, $-N(R^0)C(O)N(R^0)_2$, $-SO_2N(R^0)(CH_2CF_3)$, $-SO_2NH$(cyclopropyl), and $-SO_2N(R^0)-C(O)R^0$.

The compounds of this invention generally may be prepared from known or readily prepared starting materials, following methods known to those skilled in the art, such as those illustrated by general Scheme I below, wherein R corresponds to $R_3-(Y)_m-$ in formula I, and by the examples described herein.

Scheme I



Other compounds of this invention may be prepared by one skilled in the art following the teachings of the specification coupled with knowledge in the art using reagents that are readily synthesized or commercially available.

Compounds of the present invention are useful as CCR5 antagonists. One aspect of the instant invention relates to methods of antagonizing CCR5 chemokine receptor activity in a biological sample comprising contacting the biological sample with compounds of formula I or pharmaceutically acceptable derivatives thereof. Another aspect of the instant invention relates to methods of antagonizing CCR5 chemokine receptor activity in a patient comprising administering to the patient with a therapeutically effective amount of compounds of formula I or pharmaceutically acceptable derivatives thereof. The antagonistic activity of the present compounds towards the chemokine

receptor CCR5 may be assayed by methods known in the art, for example, by using the methods as described in example 801.

According to one embodiment of the invention, compounds of formulae I-VII or salts thereof may be formulated into compositions. In a preferred embodiment, the composition is a pharmaceutical composition, which comprises a compound of formula I and pharmaceutically acceptable carrier, adjuvant or vehicle. In one embodiment, the composition comprises an amount of a CCR5 antagonist of the present invention effective to antagonize CCR5 chemokine receptor activity in a biological sample or in a patient. In another embodiment, compounds of this invention and pharmaceutical compositions thereof, which comprise an amount of a CCR5 antagonist of the present invetion effective to antagonize CCR5 chemokine receptor activity to treat or prevent a CCR5-mediated disease or disorder and a pharmaceutically acceptable carrier, adjuvant or vehicle, may be formulated for administration to a patient, for example, for oral administration.

The term “pharmaceutically effective amount” or “therapeutically effective amount” refers to an amount of a compound of this invention that is effective in treating a CCR5-related disease, for example a virus infection, for example an HIV infection, in a patient either as monotherapy or in combination with other agents.

The term “antagonist of CCR5 chemokine receptor” refers to a compound that binds to the chemokine receptor CCR5 but fails to elicit a response thereby blocking agonist action. The term “antagonizing CCR5 chemokine receptor” refers to binding to the receptor but failing to elicit a response thereby blocking agonist action, i.e, inhibiting a function of CCR5. For example, an antagonist of CCR5 chemokine receptor may inhibit the binding of one or more ligands (e.g., MIP-1α, RANTES, MIP-1β, and gp120) to CCR5 and/or inhibit signal transduction mediated through CCR5 (e.g., GDP/GTP exchange by CCR5-associated G proteins, intracellular calcium flux). Accordingly, CCR5-mediated processes and cellular responses (e.g., proliferation, migration, chemotactic responses, secretion or degranulation) can be inhibited with an antagonist of CCR5.

The term “CCR5 mediated disease or disorder” or “CCR5 related disease or disorder” is used herein at all occurrences to mean any disease, disorder or other deleterious condition or state in which CCR5 is known to play a role.

The term “treatment” as used herein refers to the alleviation of symptoms of a particular disorder in a patient, or the improvement of an ascertainable measurement associated with a particular disorder, and may include the suppression of symptom recurrence in an asymptomatic patient such as a patient in whom a viral infection has become latent. The term “prophylaxis” refers to preventing a disease or condition or preventing the occurrence of symptoms of such a disease or condition, in a patient. As used herein, the term “patient” refers to a mammal, including a human.

As used herein, the term “subject” refers to a patient or a biological sample. The term “biological sample”, as used herein, includes, without limitation, cell cultures or extracts thereof; preparations of an enzyme suitable for *in vitro* assay; biopsied material obtained from a mammal or extracts thereof; and blood, saliva, urine, feces, semen, tears, or other body fluids or extracts thereof.

The term “pharmaceutically acceptable carrier, adjuvant or vehicle” refers to a carrier, adjuvant or vehicle that may be administered to a patient, together with a compound of this invention, and which does not destroy the pharmacological activity thereof and is nontoxic when administered in doses sufficient to deliver a therapeutic amount of the therapeutic agent.

The term “pharmaceutically acceptable derivative” means any pharmaceutically acceptable salt, ester, salt of an ester, or other derivative of a compound of this invention which, upon administration to a recipient, is capable of providing (directly or indirectly) a compound of this invention or an inhibitorily active metabolite or residue thereof. Particularly favored derivatives are those that increase the bioavailability of the compounds of this invention when such compounds are administered to a patient (e.g., by allowing an orally administered compound to be more readily absorbed into the blood) or which enhance delivery of the parent compound to a biological

compartment (e.g., the brain or lymphatic system) relative to the parent species.

Throughout this specification, the word "comprise" or variations such as "comprises" or "comprising" will be understood to imply the inclusion of a stated integer or groups of integers but not the exclusion of any other integer or group of integers.

Pharmaceutically acceptable salts of the compounds according to the invention include those derived from pharmaceutically acceptable inorganic and organic acids and bases. Examples of suitable acids include hydrochloric, hydrobromic, sulfuric, nitric, perchloric, fumaric, maleic, phosphoric, glycollic, lactic, salicyclic, succinic, toluene-p-sulfonic, tartaric, acetic, citric, methanesulfonic, ethanesulfonic, formic, benzoic, malonic, naphthalene-2-sulfonic and benzenesulfonic acids. Other acids, such as oxalic, while not in themselves pharmaceutically acceptable, may be employed in the preparation of salts useful as intermediates in obtaining the compounds of the invention and their pharmaceutically acceptable acid addition salts.

Salts derived from appropriate bases include alkali metal (e.g. sodium), alkaline earth metal (e.g., magnesium), ammonium, NW_4^+ (wherein W is C_{1-4} alkyl) and other amine salts. Physiologically acceptable salts of a hydrogen atom or an amino group include salts of organic carboxylic acids such as acetic, lactic, tartaric, malic, isethionic, lactobionic and succinic acids; organic sulfonic acids such as methanesulfonic, ethanesulfonic, benzenesulfonic and p-toluenesulfonic acids and inorganic acids such as hydrochloric, sulfuric, phosphoric and sulfamic acids. Physio-logically acceptable salts of a compound with a hydroxy group include the anion of said compound in combination with a suitable cation such as Na^+, NH_4^+, and NW_4^+ (wherein W is a C_{1-4}alkyl group).

Any reference to any of the above compounds also includes a reference to a pharmaceutically acceptable salt thereof.

Salts of the compounds of the present invention may be made by methods known to a person skilled in the art. For example, treatment of a

compound of the present invention with an appropriate base or acid in an appropriate solvent will yield the corresponding salt.

Esters of the compounds of the present invention are independently selected from the following groups: (1) carboxylic acid esters obtained by esterification of the hydroxy groups, in which the non-carbonyl moiety of the carboxylic acid portion of the ester grouping is selected from straight or branched chain alkyl (for example, acetyl, n-propyl, t-butyl, or n-butyl), alkoxyalkyl (for example, methoxymethyl), aralkyl (for example, benzyl), aryloxyalkyl (for example, phenoxymethyl), aryl (for example, phenyl optionally substituted by, for example, halogen, C_{1-4}alkyl, or C_{1-4}alkoxy or amino); (2) sulfonate esters, such as alkyl- or aralkylsulfonyl (for example, methanesulfonyl); (3) amino acid esters (for example, L-valyl or L-isoleucyl); (4) phosphonate esters and (5) mono-, di- or triphosphate esters. The phosphate esters may be further esterified by, for example, a C_{1-20} alcohol or reactive derivative thereof, or by a 2,3-di (C_{6-24})acyl glycerol.

In such esters, unless otherwise specified, any alkyl moiety present advantageously contains from 1 to 18 carbon atoms, particularly from 1 to 6 carbon atoms, more particularly from 1 to 4 carbon atoms, Any cycloalkyl moiety present in such esters advantageously contains from 3 to 6 carbon atoms. Any aryl moiety present in such esters advantageously comprises a phenyl group.

The present invention features compounds according to the invention for use in medical therapy, for example for the treatment including prophylaxis of CCR5-related diseases and disorders, including but not limited to, viral infections such as an HIV infection and associated conditions.

As discussed above, the compounds of the present invention are CCR5 antagonists. Accordingly, these compounds are capable of targeting and inhibiting the entry of a virus, e.g, HIV, into its target cell. The compounds according to the invention are especially useful for the treatment of AIDS and related clinical conditions such as AIDS related complex (ARC), progressive generalized lymphadenopathy (PGL), Kaposi's sarcoma, thromobocytopenic purpura, AIDS-related neurological conditions such as

AIDS dementia complex, multiple sclerosis or tropical paraperesis, anti-HIV antibody-positive and HIV-positive conditions, including such conditions in asymptomatic patients.

According to another aspect, the present invention provides a method for the treatment including prevention of the symptoms or effects of a viral infection in an infected patient, for example, a mammal including a human, which comprises treating said patient with a pharmaceutically effective amount of a compound according to the invention. According to one aspect of the invention, the viral infection is a retroviral infection, in particular an HIV infection. A further aspect of the invention includes a method for the treatment including prevention of the symptoms or effects of an HBV infection.

The compounds according to the invention may also be used in adjuvant therapy in the treatment of HIV infections or HIV-associated symptoms or effects, for example Kaposi's sarcoma.

The compounds of the present invention may also be used in the treatment (including prevention) of other CCR5-related diseases and conditions, including multiple sclerosis, rheumatoid arthritis, autoimmune diabetes, chronic implant rejection, asthma and topic disorders (for example, atopic dermatitis and allergies), rheumatoid arthritis, Crohns Disease, inflammatory bowel disease, chronic inflammatory disease, glomerular disease, nephrotoxic serum nephritis, kidney disease, Alzheimer's Disease, autoimmune encephalomyelitis, arterial thrombosis, allergic rhinitis, arteriosclerosis, Sjogren's syndrome (dermatomyositis), systemic lupus erythematosus, graft rejection, cancers with leukocyte infiltration of the skin or organs, human papilloma virus infection, prostate cancer, wound healing, amyotrophic lateral sclerosis, psoriasis, multiple sclerosis, chronic obstructive pulmonary disease (COPD), sarcoidosis, immune-mediated disorders, and bacterial infections, including bubonic and pneumonic plague, particularly infections of Yersinia pestis.

The present invention further provides a method for the treatment of a clinical condition in a patient, for example, a mammal including a human which clinical condition includes those which have been discussed

hereinbefore, which comprises treating said patient with a pharmaceutically effective amount of a compound according to the invention. The present invention also includes a method for the treatment including prophylaxis of any of the aforementioned diseases or conditions.

In yet a further aspect, the present invention provides the use of a compound according to the invention in the manufacture of a medicament for the treatment including prophylaxis of any of the above mentioned CCR5-related diseases or conditions including viral infections (e.g., HIV infection) and associated conditions.

Reference herein to treatment extends to prophylaxis as well as the treatment of established conditions, disorders and infections, symptoms thereof, and associated clinical conditions.

The above compounds according to the invention and their pharmaceutically acceptable derivatives may be employed in combination with other therapeutic agents for the treatment of the above infections or conditions. Combination therapies according to the present invention comprise the administration of a compound of the present invention or a pharmaceutically acceptable derivative thereof and another pharmaceutically active agent. The active ingredient(s) and pharmaceutically active agents may be administered simultaneously (i.e., concurrently) in either the same or different pharmaceutical compositions or sequentially in any order. The amounts of the active ingredient(s) and pharmaceutically active agent(s) and the relative timings of administration will be selected in order to achieve the desired combined therapeutic effect.

Examples of such therapeutic agents include, but are not limited to, agents that are effective for the treatment of viral infections or associated conditions. Among these agents are (1-alpha, 2-beta, 3-alpha)-9-[2,3-bis(hydroxymethyl)cyclobutyl]guanine [(-)BHCG, SQ-34514, lobucavir]; 9-[(2R,3R,4S)-3,4-bis(hydroxy methyl)2-oxetanosyl]adenine (oxetanocin-G); acyclic nucleosides, for example acyclovir, valaciclovir, famciclovir, ganciclovir, and penciclovir; acyclic nucleoside phosphonates, for example (S)-1-(3-hydroxy-2-phosphonyl-methoxypropyl) cytosine (HPMPC), [[[2-(6-

amino-9H-purin-9-yl)ethoxy] methyl]phosphinylidene] bis(oxymethylene)-2,2-dimethyl propanoic acid (bis-POM PMEA, adefovir dipivoxil), [[(1R)-2-(6-amino-9H-purin-9-yl)-1-methylethoxy]methyl] phosphonic acid (tenofovir), and (R)-[[2-(6-Amino-9H-purin-9-yl)-1-methylethoxy]methyl]phosphonic acid bis-(isopropoxycarbonyloxymethyl)ester (bis-POC-PMPA); ribonucleotide reductase inhibitors, for example 2-acetylpyridine 5-[(2-chloroanilino)thiocarbonyl) thiocarbonohydrazone and hydroxyurea; nucleoside reverse transcriptase inhibitors, for example 3'-azido-3'-deoxythymidine (AZT, zidovudine), 2',3'-dideoxycytidine (ddC, zalcitabine), 2',3'-dideoxyadenosine, 2',3'-dideoxyinosine (ddI, didanosine), 2',3'-didehydrothymidine (d4T, stavudine), (-)-beta-D-2,6-diaminopurine dioxolane (DAPD), 3'-azido-2',3'-dideoxythymidine-5'-H-phosphophonate (phosphonovir), 2'-deoxy-5-iodo-uridine (idoxuridine), (-)-cis-1-(2-hydroxymethyl)-1,3-oxathiolane 5-yl)-cytosine (lamivudine), cis-1-(2-(hydroxymethyl)-1,3-oxathiolan-5-yl)-5-fluorocytosine (FTC), 3'-deoxy-3'-fluorothymidine, 5-chloro-2',3'-dideoxy-3'-fluorouridine, (-)-cis-4-[2-amino-6-(cyclo-propylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol (abacavir), 9-[4-hydroxy-2-(hydroxymethyl)but-1-yl]-guanine (H2G), ABT-606 (2HM-H2G) and ribavirin; protease inhibitors, for example indinavir, ritonavir, nelfinavir, amprenavir, saquinavir, fosamprenavir, (R)-N-tert-butyl-3-[(2S,3S)-2-hydroxy-3-N-[(R)-2-N-(isoquinolin-5-yloxyacetyl)amino-3-methylthio-propanoyl]amino-4-phenylbutanoyl]-5,5-dimethyl-1,3-thiazolidine-4-carboxamide (KNI-272), 4R-(4alpha, 5alpha,6beta)]-1,3-bis[(3-aminophenyl)methyl]hexahydro-5,6-dihydroxy-4,7-bis(phenylmethyl)-2H-1,3-diazepin-2-one dimethanesulfonate (mozenavir), 3-[1-[3-[2-(5-trifluoromethylpyridinyl)-sulfonylamino]phenyl]propyl]-4- hydroxy-6alpha-phenethyl-6beta-propyl-5,6-dihydro-2-pyranone (tipranavir), N'-[2(S)-Hydroxy-3(S)-[N-(methoxycarbonyl)-l-tert-leucylamino]-4-phenylbutyl-N ^{alpha}-(methoxycarbonyl)-N'-[4-(2-pyridyl)benzyl]-L- tert-leucylhydrazide (BMS-232632), 3-(2(S)-Hydroxy-3(S)-(3-hydroxy-2-methylbenzamido)-4-phenylbutanoyl)-5,5-dimethyl-N-(2-methylbenzyl)thiazolidine-4(R)-carboxamide (AG-1776), N-(2(R)-hydroxy-1(S)-indanyl)-2(R)-phenyl-methyl-4(S)-hydroxy-5-(1-(1-(4-

benzo[b]furanylmethyl)-2(S)-N'-(tert-butyl carboxamido)piperazinyl)pentanamide (MK-944A); interferons such as α-interferon; renal excretion inhibitors such as probenecid; nucleoside transport inhibitors such as dipyridamole, pentoxifylline, N-acetylcysteine (NAC), Procysteine, α-trichosanthin, phosphonoformic acid; as well as immunomodulators such as interleukin II or thymosin, granulocyte macrophage colony stimulating factors, erythropoetin, soluble CD_4 and genetically engineered derivatives thereof; non-nucleoside reverse transcriptase inhibitors (NNRTIs), for example nevirapine (BI-RG-587), alpha-((2-acetyl-5-methylphenyl)amino)-2,6-dichloro-benzeneacetamide (loviride), 1-[3-(isopropyl amino)-2-pyridyl]-4-[5-(methanesulfonamido)-1H-indol-2-ylcarbonyl]piperazine monomethanesulfonate (delavirdine), (10R, 11S, 12S)-12-Hydroxy-6, 6, 10, 11-tetramethyl-4-propyl-11,12-dihydro-2H, 6H, 10H-benzo(1, 2-b:3, 4-b':5, 6-b")tripyran-2-one ((+) calanolide A), (4S)-6-Chloro-4-[1E)-cyclopropyl ethenyl)-3,4- dihydro-4-(trifluoromethyl)-2(1H)-quinazolinone (DPC-083), (S)-6-chloro-4-(cyclopropyl ethynyl)-1,4-dihydro-4-(trifluoromethyl)-2H-3,1-benzoxazin-2-one (efavirenz, DMP 266), 1-(ethoxy methyl)-5-(1-methylethyl)-6-(phenylmethyl)-2,4(1H,3H)-pyrimidinedione (MKC-442), and 5-(3,5-dichloro phenyl)thio-4-isopropyl-1-(4-pyridyl)methyl-1H-imidazol-2-ylmethyl carbamate (capravirine); glycoprotein 120 antagonists, for example PRO-2000, PRO-542 and 1,4-bis[3-[(2, 4- dichlorophenyl)carbonyl amino]-2-oxo-5,8-disodiumsulfanyl]naphthalyl-2, 5-dimethoxyphenyl-1, 4-dihydrazone (FP-21399); cytokine antagonists, for example reticulose (Product-R), 1,1'-azobis-formamide (ADA), 1,11-(1,4-phenylenebis (methylene))bis-1,4,8,11-tetraazacyclotetradecane octahydrochloride (AMD-3100); integrase inhibitors; and fusion inhibitors, for example T-20 and T-1249.

The present invention further includes the use of a compound according to the invention in the manufacture of a medicament for simultaneous or sequential administration with at least another therapeutic agent, such as those defined hereinbefore.

Compounds of the present invention may be administered with an agent known to inhibit or reduce the metabolism of compounds, for example ritonavir. Accordingly, the present invention features a method for the treatment including prophylaxis of a disease as hereinbefore described by administration of a compound of the present invention in combination with a metabolic inhibitor. Such combination may be administered simultaneously or sequentially.

In general a suitable dose for each of the above-mentioned conditions will be in the range of 0.01 to 250 mg per kilogram body weight of the recipient (e.g. a human) per day, preferably in the range of 0.1 to 100 mg per kilogram body weight per day and most preferably in the range 0.5 to 30 mg per kilogram body weight per day and particularly in the range 1.0 to 20 mg per kilogram body weight per day. Unless otherwise indicated, all weights of active ingredient are calculated as the parent compound of formula (I); for salts or esters thereof, the weights would be increased proportionally. The desired dose may be presented as one, two, three, four, five, six or more sub-doses administered at appropriate intervals throughout the day. In some cases the desired dose may be given on alternative days. These sub-doses may be administered in unit dosage forms, for example, containing 10 to 1000 mg or 50 to 500 mg, preferably 20 to 500 mg, and most preferably 50 to 400 mg of active ingredient per unit dosage form.

While it is possible for the active ingredient to be administered alone, it is preferable to present it as a pharmaceutical composition. The compositions of the present invention comprise at least one active ingredient, as defined above, together with one or more acceptable carriers thereof and optionally other therapeutic agents. Each carrier must be acceptable in the sense of being compatible with the other ingredients of the composition and not injurious to the patient.

Phamaceutical compositions include those suitable for oral, rectal, nasal, topical (including transdermal, buccal and sublingual), vaginal or parenteral (including subcutaneous, intramuscular, intravenous, intradermal, and intravitreal) administration. The compositions may conveniently be

presented in unit dosage form and may be prepared by any methods well known in the art of pharmacy. Such methods represent a further feature of the present invention and include the step of bringing into association the active ingredients with the carrier, which constitutes one or more accessory ingredients. In general, the compositions are prepared by uniformly and intimately bringing into association the active ingredients with liquid carriers or finely divided solid carriers or both, and then if necessary shaping the product.

The present invention further includes a pharmaceutical composition as hereinbefore defined wherein a compound of the present invention or a pharmaceutically acceptable derivative thereof and another therapeutic agent are presented separately from one another as a kit of parts.

Compositions suitable for transdermal administration may be presented as discrete patches adapted to remain in intimate contact with the epidermis of the recipient for a prolonged period of time. Such patches suitably contain the active compound 1) in an optionally buffered, aqueous solution or 2) dissolved and/or dispersed in an adhesive or 3) dispersed in a polymer. A suitable concentration of the active compound is about 1% to 25%, preferably about 3% to 15%. As one particular possibility, the active compound may be delivered from the patch by electrotransport or iontophoresis as generally described in Pharmaceutical Research 3(6), 318 (1986).

Pharmaceutical compositions of the present invention suitable for oral administration may be presented as discrete units such as capsules, caplets, cachets or tablets each containing a predetermined amount of the active ingredients; as a powder or granules; as a solution or a suspension in an aqueous or non-aqueous liquid; or as an oil-in-water liquid emulsion or a water-in-oil liquid emulsion. The active ingredient may also be presented as a bolus, electuary or paste.

A tablet may be made by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine the active ingredients in a free-flowing form such as a powder or granules, optionally mixed with a binder (e.g. povidone, gelatin, hydroxypropylmethyl cellulose), lubricant, inert diluent,

preservative, disintegrant (e.g. sodium starch glycollate, cross-linked povidone, cross-linked sodium carboxymethyl cellulose) surface-active or dispersing agent. Molded tablets may be made by molding a mixture of the powdered compound moistened with an inert liquid diluent in a suitable machine. The tablets may optionally be coated or scored and may be formulated so as to provide slow or controlled release of the active ingredients therein using, for example, hydroxypropylmethyl cellulose in varying proportions to provide the desired release profile. Tablets may optionally be provided with an enteric coating, to provide release in parts of the gut other than the stomach.

Pharmaceutical compositions suitable for topical administration in the mouth include lozenges comprising the active ingredients in a flavored base, usually sucrose and acacia or tragacanth; pastilles comprising the active ingredient in an inert basis such as gelatin and glycerin, or sucrose and acacia; and mouthwashes comprising the active ingredient in a suitable liquid carrier.

Pharmaceutical compositions suitable for vaginal administration may be presented as pessaries, tampons, creams, gels, pastes, foams or spray Pharmaceutical compositions containing in addition to the active ingredient such carriers as are known in the art to be appropriate.

Pharmaceutical compositions for rectal administration may be presented as a suppository with a suitable carrier comprising, for example, cocoa butter or a salicylate or other materials commonly used in the art. The suppositories may be conveniently formed by admixture of the active combination with the softened or melted carrier(s) followed by chilling and shaping in molds.

Pharmaceutical compositions suitable for parenteral administration include aqueous and nonaqueous isotonic sterile injection solutions which may contain anti-oxidants, buffers, bacteriostats and solutes which render the pharmaceutical composition isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents; and liposomes or other

microparticulate systems which are designed to target the compound to blood components or one or more organs. The pharmaceutical compositions may be presented in unit-dose or multi-dose sealed containers, for example, ampoules and vials, and may be stored in a freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid carrier, for example water for injection, immediately prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules and tablets of the kind previously described.

Unit dosage pharmaceutical compositions include those containing a daily dose or daily subdose of the active ingredients, as hereinbefore recited, or an appropriate fraction thereof.

It should be understood that in addition to the ingredients particularly mentioned above the pharmaceutical compositions of this invention may include other agents conventional in the art having regard to the type of pharmaceutical composition in question, for example, those suitable for oral administration may include such further agents as sweeteners, thickeners and flavoring agents.

In order that the invention described herein may be more fully understood, the following examples are set forth. It should be understood that these examples are for illustrative purposes only and are not to be construed as limiting this invention in any manner.

EXAMPLES

General Procedures

Plate purification chromatographic conditions:

Prep. HPLC Conditions A

Approximately 100 milligrams of the impure compound was dissolved in 500 microliters of methanol. This 500 microliter solution was injected by a Waters 2767 autosampler into a Phenomenex Luna C18 5 micron particle HPLC column (21.20 mm X 150 mm). Initial solvent flow was 20ml/min with 30% methanol and 70% water at a pH of 2.5 using formic acid as buffer. Void

volume was 2 minutes, and a linear gradient to 100% methanol in 10 minutes with a five minute wash at 100% methanol eluted the compound in approximately 10 minutes. A Micromass Platform LC mass spectrometer was used to monitor a split off the eluate for desired mass, and the purified fractions were collected using Micromass Fractionlynx software. About 35 mg of purified compound was isolated.

Prep. HPLC Conditions B

Approximately 100 milligrams of the impure compound was dissolved in 300 microliters of DMSO and brought up to a final volume of 500 microliters using methanol. This 500 microliter solution was injected by a Waters 2767 autosampler into an XTerra C18 5 micron particle HPLC column (19mmX150mm). Initial solvent flow was 20 ml/min with 30% methanol and 70% water at a pH of 11 using ammonium hydroxide as buffer. Void volume was 2 minutes, and a linear gradient to 100% methanol in 10 minutes with a five minute wash at 100% methanol eluted the compound in approximately 10 minutes. A Micromass Platform LC mass spectrometer was used to monitor a split off the eluate for desired mass, and the purified fractions were collected using Micromass Fractionlynx software. About 35 mg of purified compound was isolated.

Analytical and Preparative C18 HPLC chromatography

Method W

Analytical High Pressure Liguid Chromotography data was aquired using a Waters LC-UV system. The system operated using a Waters Symmetry Shield RP18 3.9 x 150 mm, 5 μm column at 1.5 mL/minute. The mobile phase consisted of Water (0.1% DEA) and Acetonitrile (0.1% DEA). The gradient used started with a 10% ACN (0.1% DEA): 90% H2O (0.1% DEA) and moved to 90% ACN (0.1% DEA):10% H2O (0.1% DEA) over 7 minutes. There was a one minute wash of the column using 100% ACN (0.1% DEA) for one minute, until eight minutes and then original conditions returned at 8.1 minutes to 8.5 minutes.

Method Y

Preparative High Pressure Liquid Chromatography data was acquired using a Waters LC-UV system. The system operated using a Waters Symmetry Shield RP18 3.9 x 150 mm, 5 μm column at 35 mL/minute. The mobile phase consisted of Water (0.1% DEA) and Acetonitrile (0.1% DEA). The gradient used started with a 10% ACN (0.1% DEA):90% H_2O (0.1% DEA) and moved to 90% ACN (0.1% DEA):10% H_2O (0.1% DEA) over 7 minutes. There was a one minute wash of the column using 100% ACN (0.1% DEA) for one minute, until eight minutes and then original conditions returned at 8.1 minutes to 8.5 minutes.

Low resolution, open-access LC-MS data were acquired in either ESI pos/neg or APCI pos/neg mode with scanning from 100-1100 amu @ 0.5 sec/scan.

LC conditions: flowrate 0.8 mL/min. 85% H2O (0.1% formic acid) to 100% MeOH (0.075% formic acid) in 6 minutes. Phenomenex Max-RP column, 2.0x50 mm.

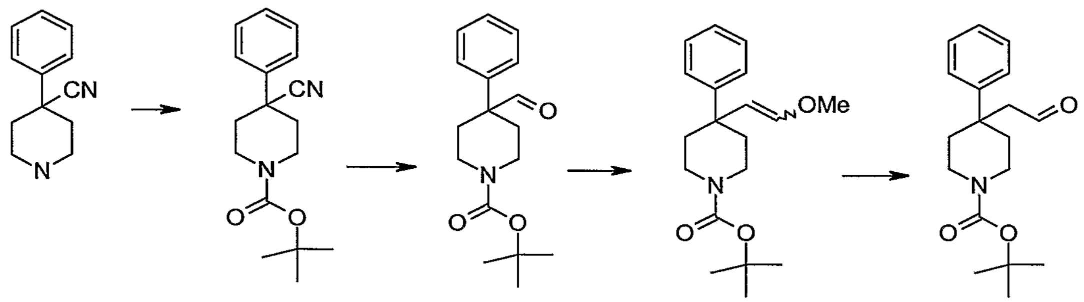
High Resolution Mass Spectra were acquired using Micromass LCT mass spectrometer (time-of-flight) with flow injection (FIA-MS) at 0.3 mL/min with 100% MeOH (0.1% formic acid), run time of 2 minutes, in ESI+ mode, scanning from 100-1100 amu @ 0.5 sec/scan.

Reserpine was used as the lock mass (m/z 609.2812) and to adjust mass scale.

Example 1

Compound IV of Scheme I was synthesized according to the procedure outlined in Scheme II below.

Scheme II



1 1a 1b 1c V

Tert-Butyl 4-cyano-4-phenylpiperidine-1-carboxylate (**1a**)

To a suspension of 4-cyano-4-phenylpiperidine hydrochloride (50.4 g, 0.266 mol) in tetrahydrofuran (440 ml) was added triethylamine (95 ml), followed by addition of a solution of di-tert-butyl dicarbonate (47.95 g, 0.22mol) in tetrahydrofuran (150 ml) dropwise. The reaction mixture was stirred at room temperature for 2 hours. The solids were filtered and the filtrate was diluted with 200 ml of ethyl acetate, washed once with 200 ml of 1N citric acid, once with 200 ml of saturated aqueous sodium bicarbonate and once with 200 ml of brine. After drying over sodium sulfate, the solution was concentrated to a colorless thick oil (64.40 g, 99%). ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.51-7.34 (m, 5H), 4.33-4.18 (m, 2H), 3.27-3.19 (m, 2H), 2.14-1.92 (m, 4H), and 1.51 (s, 9H). ES-LCMS *m/z* 308 (M+H).

Tert-Butyl 4-formyl-4-phenylpiperidine-1-carboxylate (**1b**)

To a solution of tert-butyl 4-cyano-4-phenylpiperidine-1-carboxylate (33.32 g. 0.116 mol) in toluene (600 ml), cooled to –78 °C was added a 1M solution of diisobutylaluminum hydride in toluene (248 ml) over a period of 3 h. The reaction mixture was allowed to warm up to –35 °C over a period of 2 h and stirred at –35 °C for 1 hour. The reaction mixture was quenched by dropwise addition of 150 ml of methanol, followed by addition of 150 ml of saturated aqueous ammonium chloride and filteration through Celite. The organic layer was washed once with 200 ml of water, once with 200 ml of brine and after drying over sodium sulfate, the solution was concentrated to a

light yellow oil (29.71 g, 88%). ^{1}H-NMR (300 MHz, $CDCl_3$): δ 9.43 (s, 1H), 7.55-7.18 (m, 5H), 3.92-3.82 (m, 2H), 3.31-3.18 (m, 2H), 2.40-1.92 (m, 4H), and 1.38 (s, 9H). ES-LCMS *m/z* 290 (M+H).

Tert-Butyl 4-[(E/Z)-2-methoxyethenyl]-4-phenylpiperidine-1-carboxylate (**1c**)

To a slurry of (methoxymethyl)triphenyl-phosphonium chloride (7.39 g, 21.56 mmol) in tetrahydrofuran (90 ml) was added a 1M solution of potassium tert-butoxide in tetrahydrofuran (22 ml) dropwise. The reaction mixture was stirred at room temperature for 30 minutes and a solution of tert-butyl 4-formyl-4-phenylpiperidine-1-carboxylate (6.24 g, 21.56 mmol) in tetrahydrofuran (18 ml) was added dropwise. The mixture was stirred at room temperature for 16 hours and then heated to reflux for 2 hours. The mixture was allowed to cool to room temperature, diluted with 100 ml of water and 100 ml of ethyl acetate. The aqueous layer was extracted twice with 100 ml portions of ethyl acetate and washed once with 100 ml of brine. After drying over sodium sulfate, the solution was concentrated to a brown oil, which was further purified by column chromatography on silica gel. Elution with a gradient of 10-40% ethyl acetate in hexanes afforded a 1:1 mixture of E/Z isomers as a light yellow oil (4.64 g, 68%). ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.51-7.19 (m, 5H), 6.07 and 4.84 (d, J=13.0 Hz, 1H), 5.95 and 4.23 (d, J=7.1 Hz, 1H), 3.95-3.78 (m, 2H), 3.54 and 3.51 (s, 3H), 3.30-3.06 (m, 2H), 2.20-2.09 (m, 2H), 1.98-1.76 (m, 2H), and 1.52 and 1.49 (s, 9H). ES-LCMS *m/z* 318 (M+H).

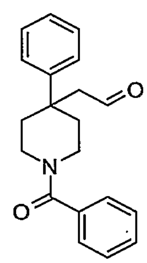
Tert-Butyl 4-(2-oxoethyl)-4-phenylpiperidine-1-carboxylate (Compound V)

To a solution of tert-butyl 4-[(E/Z)-2-methoxyethenyl]-4-phenylpiperidine-1-carboxylate
(4.64 g, 14.61 mmol) in acetone (48 ml) was added dropwise a solution of p-toluenesulfonic acid monohydrate(1.95 g, 10.28 mmol) in water (24 ml). The reaction mixture was stirred at room temperature for 48 hours. Acetone was evaporated without using any heat, and the reaction mixture was made basic

with solid sodium bicarbonate to pH 9, extracted with three 30 ml portions of dichloromethane and washed once with 30 ml of brine. After drying over sodium sulfate, the solution was concentrated to a colorless oil, which was further purified by column chromatography on silica gel. Elution with 25% ethyl acetate in hexanes afforded the product (2.23 g, 50%). ^{1}H-NMR (300 MHz, $CDCl_3$): δ 9.39 (s, 1H), 7.43-7.25 (m, 5H), 3.69-3.61 (m, 2H), 3.31-3.22 (m, 2H), 2.65 (s, 2H), 2.28-2.23 (m, 2H), 1.92-1.83 (m, 2H), and 1.46 (s, 9H). ES-LCMS *m/z* 304 (M+H).

<u>(1-Benzoyl-4-phenylpiperidine-4-yl) acetaldehyde (**2**)</u>

(1-Benzoyl-4-phenylpiperidine-4-yl) acetaldehyde (**2**) was synthesized according to the procedure outlined below.



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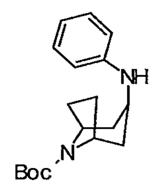
To a solution of tert-butyl 4-[(E/Z)-2-methoxyethenyl]-4-phenylpiperidine-1-carboxylate (8.75 g, 27.57 mmol) obtained by following the procedure outlined in example 1c above in tetrahydrofuran (27 ml) was added a 4M solution of hydrochloric acid in dioxane (9 ml). The reaction mixture was stirred at room temperature for 1 hour and concentrated to an oil. The mixture was dissolved in dichloromethane (40 ml) and cooled to 0 °C. A solution of benzoyl chloride (4.65 g, 33.08 mmol) in dichloromethane (5 ml)was added dropwise, followed by the addition of triethylamine 8.37 g, 82.71 mmol) in dichloromethane (5 ml). The mixture was stirred at room temperature for 1 hour, quenched by addition of 5 ml water, and washed once with 150 ml of saturated aqueous sodium bicarbonate and once with 150 ml of brine. After drying over sodium sulfate, the solution was concentrated to an oil, which was further purified by column chromatography on silica gel. Elution with a gradient of 25-50% ethyl acetate in hexanes afforded a light yellow oil (3.47 g,

41%). ^{1}H-NMR (300 MHz, $CDCl_3$): δ 9.37 (s, 1H), 7.42-7.25 (m, 10H), 4.14-4.09 (m, 1H), 3.54-3.30 (m, 3H), 2.67 (s, 2H), 2.38-2.24 (m, 2H), and 1.97-1.85 (m, 2H). ES-LCMS *m/z* 308 (M+H).

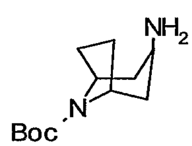
<u>The synthesis of endo 1-(8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1H-benzimidazole dihydrochloride (compound IV of Scheme I):</u>

a) *endo tert-Butyl 3-Anilino-8-azabicyclo[3.2.1]octane-8-carboxylate*



Sodium triacetoxyborohydride (125 g, 0.59 mol) was added portionwise during 45 min to a mechanically stirred mixture of *tert*-butyl 3-oxo-8-azabicyclo[3.2.1]octane-8-carboxylate (88.3 g, 0.39 mol), pulverized 4A molecular sieves (88g) and benzylamine (44.1 g, 0.41 mol) in dichloromethane (1 L) at rt under Nitrogen. The mixture was stirred at rt for 2 days. Saturated sodium carbonate solution (1 L) was added. The mixture was stirred for 1 h at room temperature, filtered and the aqueous was further extracted with dichloromethane (3 x 500 mL). The combined organic layers were dried and concentrated to a white solid (123 g, 99%). ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.24–7.33 (m, 5H), 4.19 (m, 1H), 4.10 (m, 1H), 3.76 (s, 2H), 3.00 (t, 1H), 2.15 (m, 3H), 1.91 (m, 2H), 1.60 (m, 1H), 1.57 (m, 1H), 1.49 (m, 1H), 1.48 (m, 1H), 1.45 (s, 9H). AP-LCMS *m/z* 317 (M+1).

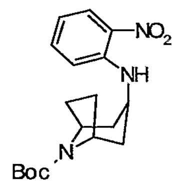
b) *endo tert-Butyl 3-Amino-8-azabicyclo[3.2.1]octane-8-carboxylate*



A stirred mixture of *tert*-butyl 3-anilino-8-azabicyclo[3.2.1]octane-8-carboxylate (123 g, 0.39 mol), ammonium formate (175 g, 2.78 mol) and 20% palladium hydroxide on carbon (12.3 g) in absolute ethanol (1.5 L) was heated to 50°C under nitrogen for 7 h. The mixture was filtered and the filtrate was

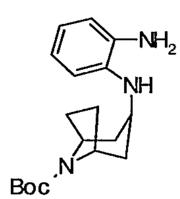
concentrated. The residue in ethyl acetate was washed with water, dried and concentrated to give the product (65.4 g, 74%). ^{1}H NMR (400 MHz; $CDCl_3$) δ 4.19 (m, 1H), 4.10 (m, 1H), 3.30 (t, 1H), 3.03–2.19 (m, 4H), 1.94 (m, 2H), 1.58 (m, 2H), 1.44 (s, 9H). AP-LCMS *m/z* 127 (M-99).

c) *endo tert-Butyl 3-[(2-Nitrophenyl)amino]-8-azabicyclo[3.2.1]octane-8-carboxylate)*



A mixture of *tert*-butyl 3-amino-8-azabicyclo[3.2.1]octane-8-carboxylate (65.4 g, 0.29 mol), *N,N*-diisopropylethylamine (56 mL, 0.32 mol) and 1-fluoro-2-nitrobenzene (40.9 g, 0.29 mol) in 1-methyl-2-pyrrolidinone (200 mL) was heated at 70°C under nitrogen for 16 h. The reaction mixture was diluted with water (500 mL) and extracted with ethyl acetate (3 x 300 mL). The combined organic layers were dried and concentrated to an orange oil. urification was accomplished by chromatography on silica gel eluting with dichloromethane and ethyl acetate:hexane 1:1 in succession to give an orange solid (98.2 g, 98%). ^{1}H NMR (400 MHz; $CDCl_3$) δ 8.74 (m, 1H), 8.18 (m, 1H), 7.43 (m, 1H), 6.61 – 6.73 (m, 2H), 4.26 (m, 2H), 3.90 (t, 1H), 2.26 – 2.32 (m, 2H), 2.03 (m, 4H), 1.83 (m, 2H), 1.44 (s, 9H).

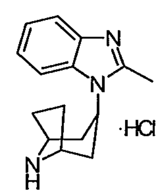
d) *endo tert-Butyl 3-[(2-Aminophenyl)amino]-8-azabicyclo[3.2.1]octane-8-carboxylate*



A mixture of *tert*-butyl 3-[(2-nitrophenyl)amino]-8-azabicyclo[3.2.1]octane-8-carboxylate (98.2 g, 0.28 mol) and 10% palladium

on carbon (10 g) in ethanol:ethyl acetate 1:1 (1 L) was hydrogenated for 24 h at atmospheric pressure. Uptake of hydrogen was 17.4 L. The mixture was filtered through celite and concentrated to give the product (76.2 g, 86%). ^{1}H NMR (400 MHz; $CDCl_3$) δ 6.67–6.83 (m, 3H), 6.57 (m, 1H), 4.25 (m, 1H), 4.17 (m, 1H), 3.70 (m, 2H), 3.32 (br s, 2H), 2.28 (m, 2H), 1.98–2.07 (m, 4H), 1.76 (m, 2H), 1.47 (s, 9H). AP-LCMS *m/z* 318 (M+1).

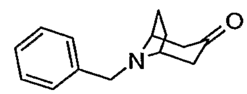
e) endo 1-(8-Azabicyclo[3.2.1]oct-3-yl)-2-methyl-1H-benzimidazole Hydrochloride



A solution of tert-butyl 3-[(2-aminophenyl) amino]-8-azabicyclo[3.2.1]octane-8-carboxylate (76.2 g, 0.24 mol) in triethylorthoacetate (250 mL) was refluxed under nitrogen for 2.5 h. The mixture was concentrated, redissolved in ethyl acetate (500 mL), washed with water (2 x 200 mL), washed with brine, dried and concentrated to a dark oil. The oil was dissolved in ethanol (250 mL), treated with 6 N hydrochloric acid (200 mL) and refluxed for 2 h. The reaction mixture was cooled to room temperature, concentrated to 300 mL and the resulting pale pink precipitate was collected by filtering, washed with ethanol (50 mL) and dried (61.5 g, 92%). ^{1}H NMR (400 MHz; DMSO-d_6) δ 10.16 (d, J=10 Hz, 1H), 9.47 (d, J=10 Hz, 1H), 7.95 (d of d, J=3,6 Hz, 1H), 7.79 (d of d, J=4,8 Hz, 1H), 7.54 (m, 2H), 5.63 (m, 1H), 4.13 (d, J=9 Hz, 2H), 2.88 (s, 3H), 2.71 (m, 2H), 2.17 (m, 6H). ES-LCMS m/z 242 (M+1).

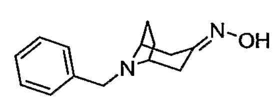
<u>The synthesis of exo-amine: exo1-(8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1H-benzimidazole</u>

8-Benzyl-8-azabicyclo[3.2.1]octan-3-one



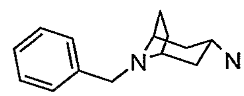
To cooled 192 ml of 0.025M HCl at 0°C was added 60 g (454 mmol) of 2,5-dimethoxytetrahydrofuran and the mixture was stirred at 0 °C for 17 hrs. Then sequentially 78g(543.6mmol) of benzyl amine, 66 g (452.0 mmol) of 3-oxopentanedioic acid, and 20.4 g (248.4 mmol) of sodium acetate in 360 ml of water was added all at 0°C. The mixture was allowed to warm to room temperature and was stirred at room temperature for 1 hr. The mixture was clear, golden yellow in color. The mixture was heated to 50 °C for 2 hrs. The mixture turned cloudy. The mixture was then cooled to ambient temperature and adjusted to pH~12 using 50% NaOH in water. The mixture was extracted with ethyl acetate (x3), dried over sodium sulfate and removed solvent to yield a brown oil. The mixture was further purified by distillation, desired product collected ~120 °C. 25 g crude product was recovered as a yellow oil to be carried on to next step.

8-Benzyl-8-azabicyclo[3.2.1]octan-3-one oxime



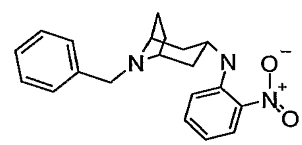
4.85 g (22.56 mmol) of 8-benzyl-8-azabicyclo[3.2.1]octan-3-one was dissolved in 60 ml of ethanol. 3.13 g (45 mmol) hydroxylamine hydrochloride was then added followed by 1.8 g (45 mmol) of NaOH in 15 ml of water. The mixture was refluxed for 20 hrs and was cooled to ambient temperature. The solvent was removed in vaccuo. The residue was diluted with ethyl acetate and washed with water and the organic layer was dried over sodium sulfate. The solvent was removed to give 4.28 g of product as a light yellow solid.

8-Benzyl-8-azabicyclo[3.2.1]octan-3-amine



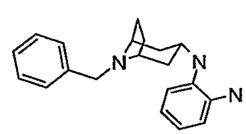
To 3.9 g (16.9mmol) 8-benzyl-8-azabicyclo[3.2.1]octan-3-one oxime was added 3.5 g of sodium in 200 ml of pentanol by portion over 1 hr. The mixture was refluxed for 3 hrs and cooled to ambient temperature. The reaction mixture was quenched with water and extracted with 6 N HCl. The aqueous layer was basified using NaOH pellets and extracted with EtOAc. The organic layer was dried over magnesium sulfate and the solvent was removed to afford 2.9 g (80%) of crude product as a brown oil.

8-Benzyl-N-(2-nitrophenyl)-8-azabicyclo[3.2.1]octan-3-amine



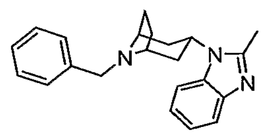
5.62g(27.82mmol) 8-benzyl-8-azabicyclo[3.2.1]octan-3-amine(u17094-94) and 9.7ml(55.46mmoml) of Hunig's base were dissolved in 200ml NMP. 4.32g(30.60mmol) 1-fluoro-2-nitrobenzene was then added and the mixture was stirred at RT for 3 hrs. The reaction mixture was diluted with EtOAc and washed with water and dried over sodium sulfate. The solvent was removed partially under reduced pressure and was left in refrigerator overnight. The solid was filtered off to afford 2.92 g of product as a yellow powder. The solvent was removed from filtration to give additional 5.7 g of product as an orange-yellow residue.

N-(8-Benzyl-8-azabicyclo[3.2.1]oct-3-yl)benzene-1,2-diamine



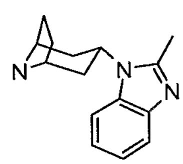
2.92 g (9.04 mmol) 8-benzyl-N-(2-nitrophenyl)-8-azabicyclo[3.2.1]octan-3-amine was dissolved in 150 ml EtOAc and 25 ml Methanol. 1g Pd/C was then added and the mixture was stirred at 1 atm H_2 for 3.5 hrs. Yellow color disappeared and the reaction mixture was filtered through celite. The solvent was removed to afford 2.2 g of desired solid.

1-(8-Benzyl-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1H-benzimidazole



7.7 g (25.08 mmol) N-(8-benzyl-8-azabicyclo [3.2.1]oct-3-yl)benzene-1,2-diamine was refluxed in 200 ml of 1,1,1-triethoxyethane for 18 hrs. The mixture was cooled to ambient temperature and the solvent was then removed. The residue was dissolved in toluene and 1.8 g (9.47 mmol) of p-toluenesulfonic acid was added and the reaction mixture was heated to reflux while stirring for 18 hrs. The mixture was cooled to ambient temperature and filtered off solid and removed toluene under reduced pressure. The crude product was purified by flash column chromatography with 5% methanol and 0.5% ammonium hydroxide in dichloromethane on silica gel. 2.2g of the product was recovered as a yellow residue.

1-(8-Azabicyclo[3.2.1]oct-3-yl)-2-methyl-1H-benzimidazole



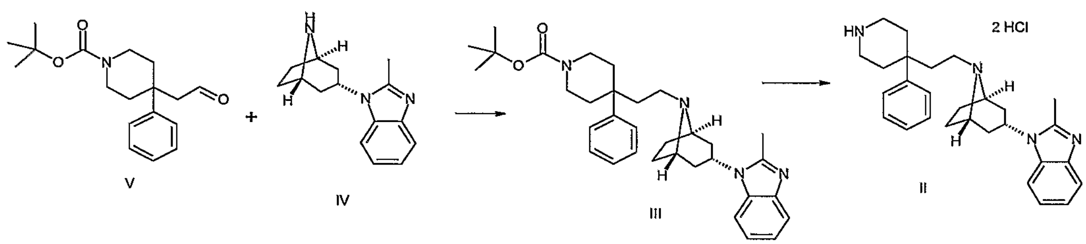
2.2 g (6.65 mmol) 1-(8-benzyl-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1H-benzimidazole was dissolved in 150 ml ethanol and 2.09 g (33.23 mmol) ammonium formate and 0.4 g palladium hydroxide (20% on carbon) were added. The mixture was refluxed for 2.5 hrs. The mixture was cooled to ambient temperature and filtered through celite. The solvent was removed

under reduced pressure and the crude product was purified by column chromatography $CH_2Cl:CH_3OH:NH_4OH$(95:5:0.5) to afford 1.06 g of the desired product as a solid.

Example 2

Endo 2-methyl-1-{8-[2-(4-phenylpiperidin-4-yl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1H-benzimidazole dihydrochloride (compound II in Scheme I) was prepared by following the procedure depicted in Scheme III below.

Scheme III



tert-butyl 4-{2-[(1R, 5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-endo-azabicyclo[3.2.1]oct-8-yl)ethyl}-4-phenylpiperidine-1-carboxylate (III)

To a solution of 483 mg (2.0 mmol) of *endo* 1-(8-Azabicyclo[3.2.1]oct-3-yl)-2-methyl-1*H*-benzimidazole dihydrochloride (IV) and of 606 mg (2.0 mmol) tert-butyl 4-(2-oxoethyl)-4-phenylpiperidine-1-carboxylate (V) in 25 mL dichloroethylene was added 847 mg (4.0 mmol) of sodium triacetoxyborohydride at room temperature and stirred for 30 minutes. The reaction was quenched with 10% aqueous sodium bicarbonate, solvents were removed and the residue partitioned between ethyl acetate and water, resulting in 925 mg of *tert*-butyl 4-{2-[(1R, 5S)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-*endo*-azabicyclo[3.2.1]oct-8-yl)ethyl}-4-phenylpiperidine-1-carboxylate III (87.6% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.21 (1H, d, *J*=8.3 Hz), 6.63-6.97 (8H, m), 4.15 (1H, m), 3.20 (2H, m), 2.78m (4H, m), 2.12 (3H, s), 1.92 (2H, m), 1.70 (2H, m), 1.45 (6H, m), 1.33 (4H, m), 1.18 (2H, m), and 1.02 (9H, s). ^{13}C NMR (400 MHz, $CDCl_3$): δ 155.2, 152.0, 144.9, 143.6, 133.8, 128.7, 126.8, 126.3, 121.6, 119.7, 111.0, 79.6, 57.4, 48.1, 46.3, 42.0, 41.0 (broad),

40.2 (broad), 39.4 (quat), 36.6, 35.8 (broad), 30.0, 28.7, and 14.9. MS ES+ (m/z) M+1 = 529.61.

endo 2-methyl-1-{8-[2-(4-phenylpiperidin-4-yl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1H-benzimidazole dihydrochloride (Compound II)

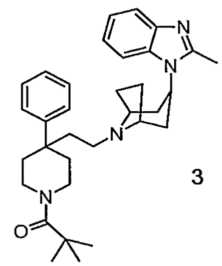
0.67g (1.27 mmol) of *tert*-butyl 4-{2-[(1R, 5S)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-*endo*-azabicyclo[3.2.1]oct-8-yl)ethyl}-4-phenylpiperidine-1-carboxylate III was dissolved in 5 mL dichloromethane and added 14 mL of 4N hydrochloric acid in dioxane. The mixture was stirred at room temperature for 30 minutes, resulting in a gummy precipitate. Solvents were decanted and the gum dried in vacuo, resulting in 0.63 g (quantitative) of *endo* 2-methyl-1-{8-[2-(4-phenylpiperidin-4-yl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1*H*-benzimidazole dihydrochloride II, which was subsequently used without additional work-up. MS ES+ (m/z) M+1 = 429.30.

Neutralization of Dihydrochloride II to Free base IIa: endo 2-Methyl-1-{8-[2-(4-phenylpiperidin-4-yl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1H-benzimidazole (Compound IIa)

2-methyl-1-{8-[2-(4-phenylpiperidin-4-yl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1H-benzimidazole dihydrochloride was partitioned between saturated sodium bicarbonate solution (300 mL) and dichloromethane (600 mL). The organic layer was dried over anhydrous sodium sulfate. After evaporation of solvents, 2-methyl-1-{8-[2-(4-phenylpiperidin-4-yl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1H-benzimidazole IIa was obtained as foam, which was used for the next step without further purification.

Example 3

1-(8-{2-[1-(2,2-Dimethylpropanoyl)-4-phenylpiperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1H-benzimidazole (**3**)

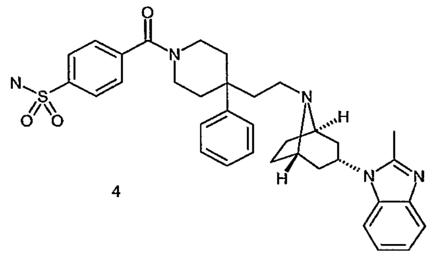


3

To a solution of *endo* 2-methyl-1-{8-[2-(4-phenylpiperidin-4-yl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1*H*-benzimidazole dihydrochloride II (0.18 g, 0.42 mmol) in dichloromethane (5 ml) was added triethylamine (0.117 ml), followed by addition of trimethylacetyl chloride (0.056 g, 0.462 mmol). The mixture was stirred at room temperature for 1 h and 0.5 ml water and 1 ml saturated aqueous sodium bicarbonate were added. The mixture was extracted three times with 5 ml of ethyl acetate and washed once with 5 ml brine. After drying over sodium sulfate, the solution was concentrated to a tan oil, which was further purified by column chromatography on silica gel. Elution with a gradient of 2.5-5% methanol in dichloromethane afforded a colorless oil (0.142 g, 66%). ^{1}H-NMR (300 MHz, DMSO-d_6) δ 7.49 (d, J=7.2 Hz, 1H), 7.40-7.35 (m, 5H), 7.23-7.20 (m, 1H), 7.14-7.08 (m, 2H), 4.54-4.50 (m, 1H), 3.80-3.76 (m, 2H), 3.34-3.23 (m, 4H), 2.49 (s, 3H), 2.38-2.32 (m, 2H), 2.09-2.05 (m, 2H), 1.87-1.74 (m, 10H), 1.59-1.57 (m, 2H), 1.18 (s, 6H), 1.11 (s, 3H). ES-LCMS *m/z* 513 (M+H). HRMS *m/z* $(M+H)^+$ calcd 513.3593, $(M+H)^+$ obsvd 513.3586.

Example 4

4-[(4-{2-[3-(2-Methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]benzene-sulfonamide (4)



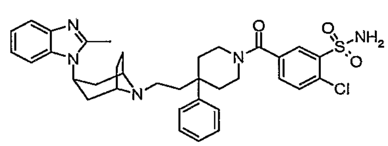
4

4-[(4-{2-[3-(2-Methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]benzenesulfonamide (25.8 mg, 83%) was obtained as amorphous solid from 2-methyl-1-{8-[2-(4-phenylpiperidin-4-yl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1*H*-benzimidazole dihydrochloride II (25.3 mg, 0.05 mmol) and *p*-carboxybenzenesulfonamide (10 mg, 0.05 mmol) by the similar procedure outlined for example 5. ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.86 (d, J=8.2 Hz, 2 H), 7.57 (d, J=8.4 Hz, 2 H), 7.49-7.47 (m, 2 H), 7.39-7.34 (m, 4 H), 7.24-7.20 (m, 1 H), 7.14-7.06 (m, 2 H), 4.52-4.47 (m, 1 H), 3.89 (br, 1 H), 3.22-3.15 (m, 6 H), 2.44 (s, 3 H), 2.42-2.30 (m, 2 H), 2.14-2.08 (br, 2 H), 1.87-1.72 (m, 10 H), 1.58 (d, J=7.6 Hz, 2 H). HRMS *m/z* $(M+H)^+$ calcd 612.3008; obsd 612.2993.

Example 5

2-chloro-5-[(4-{2-[3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl] benzenesulfonamide

example 5 via carbodiimide coupling



5

To a stirred solution of 2-methyl-1-{8-[2-(4-phenylpiperidin-4-yl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1*H*-benzimidazole dihydrochloride II (102 mg, 0.2 mmol) in dichloromethane (15 mL) was added 3-chloro-4-sulfamoylbenzoic acid (48 mg, 0.2 mmol) and triethylamine (60 μL, 0.4 mmol). The resulting

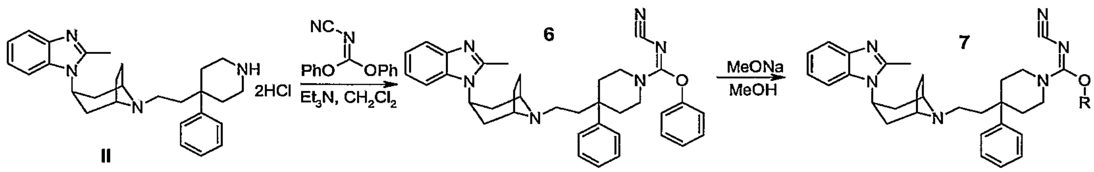
mixture was then cooled down on an ice-water bath before the addition of 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (38 mg, 0.2 mmol) and 4-dimethylaminopyridine (4.8 mg, 0.0 4mmol). After being stirred overnight at ambient temperature, the reaction mixture was diluted with dichloromethane (40 mL) and washed with saturated sodium bicarbonate solution. The organic phase was dried over anhydrous sodium sulfate. After evaporation of the solvent, the crude product was purified by flash chromatography on silical gel, eluting with a gradient of 0-10% methanol in ethyl acetate to afford 2-chloro-5-[(4-{2-[3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl] benzenesulfonamide as amorphous solid (69 mg, 53%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.87-7.71 (m, 3 H), 7.57 (s, 1 H), 7.50-7.47 (m, 2 H), 7.38-7.33 (m, 4 H), 7.24 (s, 1 H), 7.14-7.06 (m, 2 H), 4.49 (m, 1 H), 3.98 (m, 1 H), 3.42-3.23 (m, 5 H), 3.06-3.00 (m, 1 H), 2.43 (s, 3 H), 2.39-2.22 (m, 2 H), 2.17-2.08 (m, 2 H), 1.92-1.76 (m, 10 H), 1.58-1.56 (br, 2 H). HRMS *m/z* $(M+H)^+$ calcd 646.2619; obsd 646.2610.

example 5 via HATU coupling

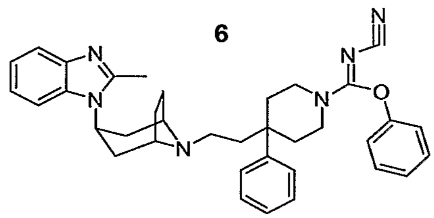
To a stirred solution of 2-methyl-1-{8-[2-(4-phenylpiperidin-4-yl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1*H*-benzimidazole dihydrochloride (200 mg, 0.4 mmol) in DMF (8 mL) was added 3-chloro-4-sulfamoylbenzoic acid (94 mg, 0.4 mmol), triethylamine (166 μL, 1.2 mmol) and HATU (152 mg, 0.4 mmol). The resulting mixture was stirred at ambient temperature for 3 hours before being diluted with methylene chloride (50 mL). The reaction was then washed with saturated sodium bicarbonate solution. The organic phase was dried over anhydrous sodium sulfate. After evaporation of the solvent, the crude product was purified by flash chromatography on silical gel, eluting with a gradient of 0-10% methanol in ethyl acetate to afford 2-chloro-5-[(4-{2-[3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl] benzenesulfonamide as amorphous solid (120 mg, 47%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.87-7.71 (m, 3 H), 7.57 (s, 1 H), 7.50-7.47 (m, 2 H), 7.38-7.33 (m, 4 H), 7.24 (s, 1 H), 7.14-7.06 (m, 2 H), 4.49

(m, 1 H), 3.98 (m, 1 H), 3.42-3.23 (m, 5 H), 3.06-3.00 (m, 1 H), 2.43 (s, 3 H), 2.39-2.22 (m, 2 H), 2.17-2.08 (m, 2 H), 1.92-1.76 (m, 10 H), 1.58-1.56 (br, 2 H). HRMS m/z $(M+H)^+$ calcd: 646.2619; obsd: 646.2610.

Example 6



Phenyl N-cyano-4-{2-[3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidine-1-carboximidoate (**6**)



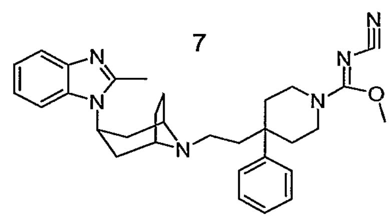
To a stirred solution of 2-methyl-1-{8-[2-(4-phenylpiperidin-4-yl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1*H*-benzimidazole dihydrochloride II (253 mg, 0.5 mmol) in dichloromethane (20 mL) was added triethyl-amine (140 μL, 1 mmol) and diphenylcyanocarbonimide (143 mg, 0.6 mmol). The resulting mixture was stirred at ambient temperature for 4 hours before it was quenched with saturated sodium bicarbonate solution. The layers were separated and the aqueous layer was extracted with dichloromethane (2 x 20 mL). The combined organic layers were dried over anhydrous sodium sulfate. After evaporation of the solvent, the residue was purified by flash chromatography on silical gel, eluting with a gradient of 0-10% methanol in ethyl acetate to afford phenyl *N*-cyano-4-{2-[3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidine-1-carboximidoate as amorphous solid (270 mg, 94%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.69-7.66 (m, 1 H), 7.41-7.36 (m, 4 H), 7.30-7.21 (m, 5 H), 7.19-7.12 (m, 2 H), 7.06-7.03 (m, 2 H), 4.65-4.58 (m, 1 H), 4.07 (br, 1 H), 3.37 (br, 2 H), 3.23 (br, 2 H), 2.56 (s,

3 H), 2.40-2.32 (m, 4 H), 1.93-1.82 (m, 11 H), 1.62 (d, *J* =7.9, 2 H). HRMS *m/z* $(M+H)^+$ calcd 573.3344; obsd 573.3348.

Example 7

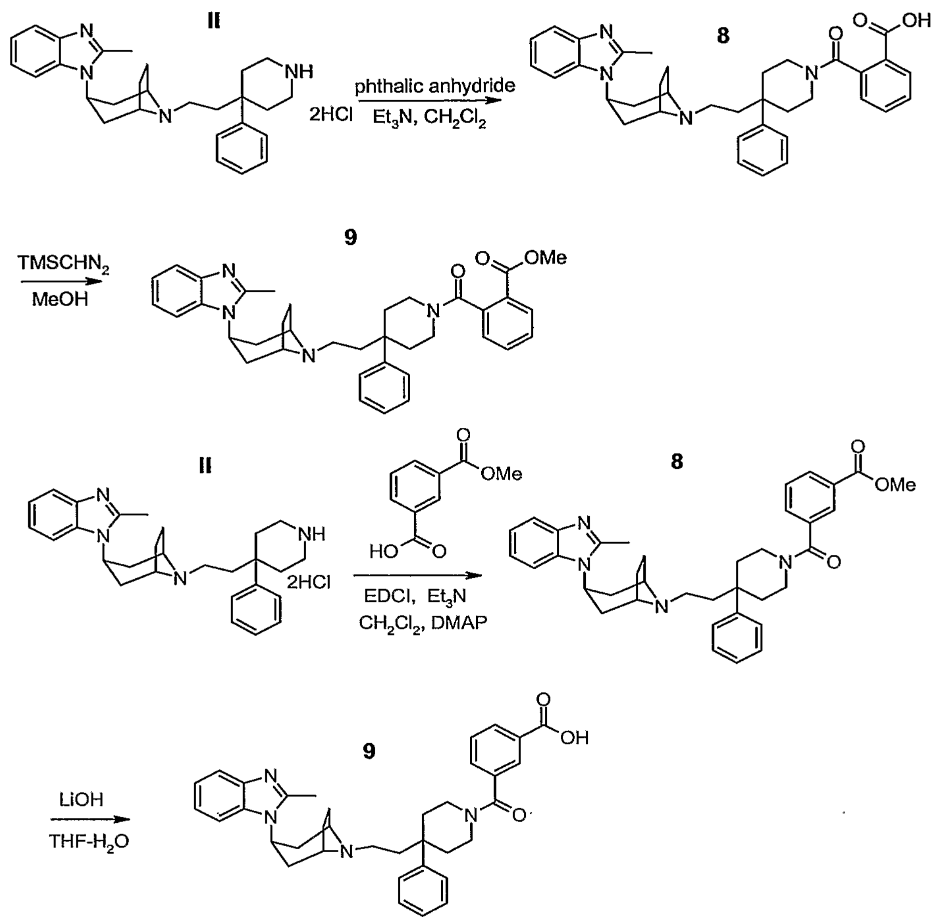
Methyl N-cyano-4-{2-[3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidine-1-carboximidoate (**7**)

7

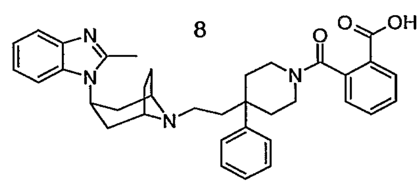


To a stirred solution of phenyl *N*-cyano-4-{2-[3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1] oct-8-yl]ethyl}-4-phenylpiperidine-1-carboximidoate **6** (35 mg, 0.06 mmol) in THF (1 mL) was added sodium methoxide in methanol (100 μL, ~0.8 M, freshly made from methanol and sodium). The resulting mixture was stirred at ambient temperature for 30 minutes before evaporation of the solvent. The crude product was then purified by flash chromatography on silical gel, eluting with a gradient of 0-15% methanol in ethyl acetate to afford methyl N-cyano-4-{2-[3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidine-1-carboximidoate as amorphous solid (21.8 mg, 72 %). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.69-7.66 (m, 1H), 7.42-7.37 (m, 2H), 7.32-7.24 (m, 4H), 7.21-7.13 (m, 2H), 4.64 (br, 1H), 4.19-4.07 (br, 2H), 3.92 (s, 3H), 3.40-3.27 (m, 4H), 2.59 (s, 3H), 2.35-2.30 (m, 4H), 1.97-1.83 (m, 10H), 1.66-1.63 (m, 2H). HRMS *m/z* $(M+H)^+$ calcd 511.3185; obsd 511.3211.

Example 8



2-[(4-{2-[3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo-[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]benzoic acid (**8**)



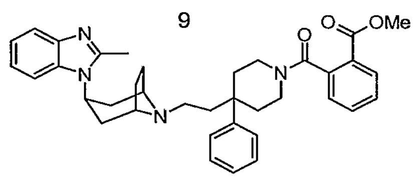
To a stirred solution of 2-methyl-1-{8-[2-(4-phenylpiperidin-4-yl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1H-benzimidazole dihydrochloride II (25.3 mg, 0.05 mmol) in 1,2-dichloroethane (3 mL) was added triethyl amine (14 μL, 0.1 mmol) and phthalic anhydride (7.4 mg, 0.05 mmol). The resulting mixture was stirred at ambient temperature for 4 hours. After evaporation of the solvents, the residue was purified by flash chromatography on silical gel, eluting with a gradient of 10-30% methanol in ethyl acetate to afford 2-[(4-{2-[3-(2-methyl-

1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1] oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]benzoic acid as amorphous solid (29 mg, quant.). ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.94 (d, J=6.6 Hz, 1H), 7.53-7.50 (m, 1H), 7.48-7.36 (m, 7H), 7.25-7.21 (m, 1H), 7.17-7.09 (m, 3H), 4.61-4.54 (m, 1H), 3.26 (br, 4H), 3.95 (br, 1H), 3.09 (br, 1H), 2.46 (s, 3H), 2.42-2.32 (m, 3H), 2.24-2.06 (m, 1H), 2.00-1.86 (m, 5H), 1.86-1.76 (m, 5H), 1.61 (d, J=7.7Hz, 2H). HRMS m/z $(M+H)^+$ calcd 577.3179; obsd 577.3176.

Example 9

methyl 2-[(4-{2-[3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]benzoate (**9**)

9

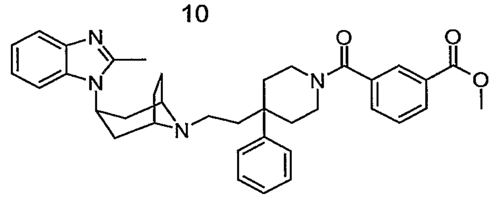


To a stirred solution of 2-[(4-{2-[3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]benzoic acid 8 (40 mg, 0.07mmol) in methanol (2 mL) was added (trimethylsilyl)diazomethane (0.35 mL, 2.0 M in hexanes). The resulting mixture was further stirred for 30 minutes. After evaporation of solvents, the residue was purified by flash chromatography on silical gel, eluting with a gradient of 0-10% methanol in ethyl acetate to afford methyl 2-[(4-{2-[3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]benzoate 9 as an oil (40 mg, quant.). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (d, J=7.6Hz, 1H), 7.64 (d, J=7.7Hz, 1H), 7.54 (s, 1H), 7.45-7.41 (m, 1H), 7.37-7.34 (m, 2), 7.29-7.21 (m, 5H), 7.18-7.10 (m, 2H), 4.63-4.53 (m, 1H), 4.21-4.18 (m, 1H), 3.86 (br, 3H), 3.44 (br, 1H), 3.24 (br, 3H), 3.08 (br, 1H), 2.53 (s, 3H), 2.36-2.34 (m, 3H), 1.91-1.71 (m, 11H), 1.59 (d, J=7.0Hz, 2H). HRMS m/z $(M+H)^+$ calcd 591.3335; obsd 591.3353.

Example 10

methyl 3-[(4-{2-[3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]benzoate (**10**)

10

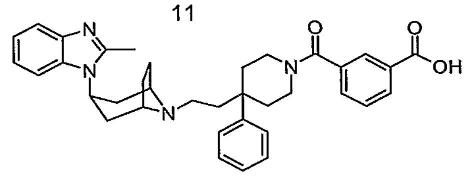


To a stirred solution of 2-methyl-1-{8-[2-(4-phenylpiperidin-4-yl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1H-benzimidazole IIa (300 mg, 0.7 mmol) in dichloromethane (10 mL) was added isophthalic acid monomethyl ester (138.9 mg, 0.77 mmol) and triethyl amine (107 μL, 0.77 mmol). The resulting mixture was then cooled down on an ice-water bath before the addition of 1-[3-(dimethylamino)propyl]-3-ethyl carbodiimide hydrochloride (146.7 mg, 0.77 mmol) and 4-dimethylaminopyridine (8.5mg. 0.07mmole). After being stirred for 4 hours at ambient temperature, the reaction mixture was quenched with saturated sodium bicarbonate solution and extracted with dichloromethane (3 X 40 mL). The combined organic phase was dried over anhydrous sodium sulfate. After evaporation of the solvent, the crude product was purified by flash chromatography on silica gel, eluting with a gradient of 0-10% methanol in ethyl acetate to afford methyl 2-[(4-{2-[3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]benzoate 10 as amorphous solid (297 mg, 72%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.13-8.08 (m, 2H), 7.70 (d, J=8.3Hz, 1H), 7.63 (d, J=7.5Hz, 1H), 7.53 (t, J=7.7 Hz, 1H), 7.45-7.40 (m, 2H), 7.35-7.30 (m, 4H), 7.20-7.15 (m, 2H), 4.68 (br, 1H), 4.2 (br, 1H), 3.96 (s, 3H), 3.57 (br, 1H), 3.43-4.31 (m, 4H), 2.60 (s, 3H), 2.42 (br, 3H), 2.19 (br, 1H), 1.99-1.92 (m, 10H), 1,69 (br, 2H). HRMS m/z $(M+H)^+$ calcd 591.33335; obsd 591.3325.

Example 11

3-[(4-{2-[3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo-[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]benzoic acid (**11**)

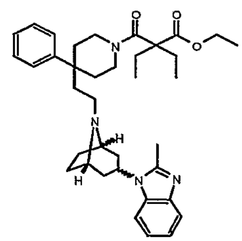
11



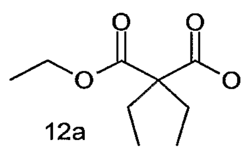
To a precooled (0 °C) stirred solution of methyl 3-[(4-{2-[3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]benzoate 10 (20 mg, 0.034mmol) in a 2 mL-mixed solvent of THF-H_2O (3:1) was added lithium hydroxide monohydrate (4.3 mg, 0.1 mmol). The resulting mixture was stirred for 2 hours at 0 °C before being buffered with saturated sodium bicarbonate solution. The reaction mixture was then extracted with dichloromethane (3 x 20 mL). The combined extracts were washed with brine and dried over anhydrous sodium sulfate. After evaporation of the solvent, the crude product was purified by flash chromatography on silical gel, eluting with a gradient of 10-30% methanol in ethyl acetate to afford 3-[(4-{2-[3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]benzoic acid **11** as white powder solid (18 mg, 95%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.98 (s, 1H), 7.91 (s, 1H), 7.51 (d, J=6.9Hz, 1H), 7.40-7.36 (m, 7H), 7.26-7.24 (m, 2H), 7.14-7.08 (m, 2H), 4.55-4.49 (m, 1H), 3.92 (br, 1H), 3.34 (br, 1H), 4.24 (br, 2H), 2.45 (s, 3H), 2.39-2.32 (m, 3H), 2.14 (br, 3H), 1.86-1.73 (m, 10H), 1.59 (d, J=7.3 Hz, 2H). HRMS m/z $(M+H)^+$ calcd 577.3179; obsd 577.3192.

Example 12

ethyl 2-ethyl-2-[(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperdin-1-yl)carbonyl]butonate (**12**)



2-(ethoxycarbonyl)-2-ethylbutanoic acid



12a

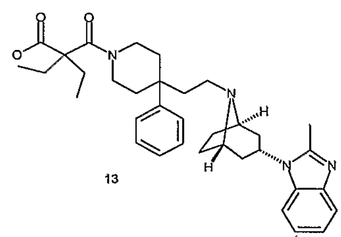
A solution of diethyl-malonic acid diethyl ester (3.0g, 13.89mmol) and potassium hydroxide (0.778g, 13.89mmol) in ethanol (50ml) was stirred at room temperature for 18 hrs. The solvent was evaporated off and the residue was dissolved in water (20 ml) and extracted with dichloromethane (20ml). This organic layer was discarded. The aqueous layer was then acidified with concentrated HCl and extracted with dichloromethane (3 x 20 ml). The combined organic layers were dried over magnesium sulfate and concentrated to give a colorless oil **12a** (1.9 g, 72%). ^{1}H NMR (300MHz, Methanol-d_4) δ 4.17 (m, 2H), 1.89 (m, 4H), 1.25 (m, 3H), 0.83 (m, 6H). ES-LCMS m/z 188 (M+H)

A solution of 2-(ethoxycarbonyl)-2-ethylbutanoic acid 12a (0.043g, 0.25mmol), 1-1'-Carbonyldiimdazole (0.048g, 0.25mmol) and 1-Hydroxybenzotriazole hydrate (0.034g, 0.25mmol) in dichloromethane (8ml) was stirred for 10 min at RT. Then 2-methyl-1-{8-[2-(4-phenylpiperidin-4-yl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1H-benzimidazole IIa (0.090g, 0.21mmol) and triethylamine (0.64g, 0.088ml, 0.63mmol) were added and stirred for 18 hrs at room temperature. The reaction was diluted with dichloromethane (10ml) and extracted 1M citric acid (3 x 10ml). The aqueous layer was neutralized with 1M sodium carbonate and extracted with dichloromethane (3

x 10ml). Organic layer was dried using magnesium sulfate and solvent evaporated to white oil. The desired product was further purified column chromatography on silica gel using an elution gradient of dichloromethane: methanol (100:0 to 90:10) to afford the product as a colorless oil (0.115g, 91%). ^{1}H NMR (300MHz, $CDCl_3$) δ 7.88 (d, 1H), 7.67 (t, 1H), 7.40-7.15 (m, 7H), 5.20-4.50 (m, 3H), 4.15 (m,3 H), 3.41 (m, 3H), 3.12 (m, 2H), 2.55 (s, 3H), 2.45 (m, 1H), 2.20-1.60 (m, 16H), 1.44 (s, 1H), 1.21 (m, 3H) 0.87 (m, 6H). HRMS $C_{37}H_{50}N_4O_3$ m/z $(M+H)_{Cal.}$ 599.3961; $(M+H)_{Obs.}$ 599.3981.

Example 13

2-ethyl-2-[(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperdin-1-yl)carbonyl]butonic acid

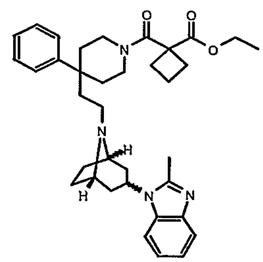


13

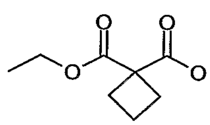
A solution of ethyl 2-ethyl-2-[(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperdin-1-yl)carbonyl]butonate 12 (0.100 g, 0.17 mmol), 5 N NaOH (10 ml) and ethanol (4 ml) was stirred at 90 °C for 3 hrs. The reaction was evaporated to dryness and residue was suspend in water (10 ml) and neutralized with 1 N HCl. The aqueous layer was extracted with ethyl acetate (3 x 10 ml). The organic layer was dried using magnesium sulfate and concentrated down to form a white oil **13** (0.060 g, 62%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.80 (d, 1H), 7.38-7.23 (m, 8H), 4.73 (m, 1H), 4.12 (m, 1H), 3.20 (m, 3H), 2.66 (s, 3H), 2.24 (m, 2H), 2.05-1.70 (m, 9H), 1.60 (m, 2H), 1.35-1.05 (m, 15H). HRMS $C_{35}H_{46}N_4O_3$ m/z $(M+H)_{Cal.}$ 571.3648; $(M+H)_{Obs.}$ 571.3650.

Example 14

Ethyl 1-[(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]cyclobutanecaboxylate



1-(ethoxycarbonyl)cyclobutanecarboxylic acid



14a

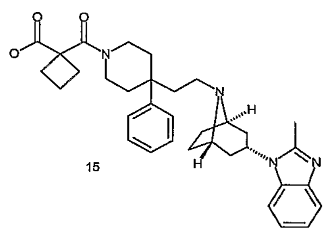
A solution of diethyl ester (1.6 g, 8.20 mmol) and potassium hydroxide (0.459 g, 8.20 mmol) in ethanol (50 ml) was stirred at room temperature for 18 hrs. The solvent was evaporated off and the residue was dissolved in water (20 ml) and extracted with dichloromethane (20 ml). This organic layer was discarded. The aqueous layer was then acidified with concentrated HCl and extracted with dichloromethane (3 x 20 ml). The combined organic layers were dried over magnesium sulfate and concentrated to give a colorless oil (0.900 g, 63%). ^{1}H NMR (300MHz, $CDCl_3$) δ 4.25 (m, 2H), 2.60 (m, 4H), 2.00 (m, 2H), 1.30 (m, 3H). ES-LCMS m/z 172 (M+H).

A solution of 1-(ethoxycarbonyl)cyclobutane carboxylic acid (0.043 g, 0.25 mmol), 1-1'-carbonyl-diimdazole (0.048 g, 0.25 mmol) and 1-Hydroxybenzo-triazole hydrate (0.034 g, 0.25 mmol) in dichloro-methane (8 ml) was stirred for 10 min at RT. Then 2-methyl-1-{8-[2-(4-phenylpiperidin-4-yl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1H-benzimidazole IIa (0.090 g, 0.21 mmol) and triethylamine (0.64 g, 0.088 ml, 0.63 mmol) were added and stirred for 18 hrs at room temperature. The reaction was diluted with dichloromethane (10 ml) and extracted 1 M citric acid (3 x 10 ml). The aqueous layer was neutralized with 1M sodium carbonate and extracted with

dichloromethane (3 x 10 ml). The organic layer was dried using magnesium sulfate and the solvent evaporated to white oil. The desired product was further purified column chromatography on silica gel using an elution gradient of dichloromethane: methanol (100:0 to 90:10) to afford the product as a colorless oil 14 (0.085g, 70%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.89 (m, 1H), 7.67 (m, 1H), 7.26 (m, 7H), 4.86 (m, 1H), 4.25-3.90 (m, 3H), 3.89 (s, 2H), 3.21 (m, 2H), 2.96 (m, 1H), 2.70-2.35 (m, 9H), 2.55-1.55 (m, 16H), 1.22 (m, 3H). HRMS $C_{36}H_{46}N_4O_3$ m/z 583.3648 $(M+H)_{Cal.}$; 583.3623 $(M+H)_{Obs.}$.

Example 15

1-[(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]cyclobutanecaboxylic acid

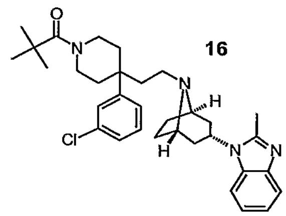


15

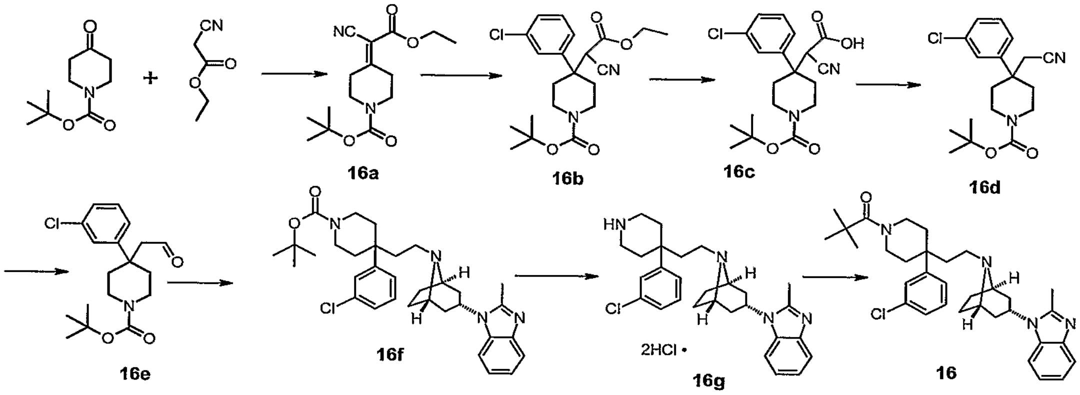
A solution of ethyl 1-[(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]cyclobutane-caboxylate from example 14 (0.050 g, 0.086 mmol), 5 N NaOH (10 ml) and ethanol (4 ml) was stirred at 90°C for 3 hrs. The reaction was evaporated to dryness and residue was suspend in water (10 ml) and neutralized with 1N HCl. The aqueous layer was extracted with ethyl acetate (3 x 10 ml). The organic layer was dried using magnesium sulfate and concentrated down to form a white oil (0.032 g, 67%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.68 (d, 1H), 7.27 (m, 8H), 4.63 (m, 1H), 3.84 (m, 1H), 3.41 (m, 1H), 3.25-2.95 (m, 4H), 2.87 (m, 1H), 2.58 (s, 3H), 2.45-2.20 (m, 4H), 2.05 (m, 2H), 1.89 (m, 8H), 1.63 (m, 5H), 1.61 (s, 2H). HRMS $C_{34}H_{42}N_4O_3$ m/z 555.3335 $(M+H)_{Cal.}$; 555.3320 $(M+H)_{Obs.}$.

Example 16

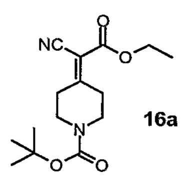
Endo-1-(8-{2-[4-(3-chlorophenyl)-1-(2,2-dimethylpropanoyl)piperidin-4-yl]ethyl}-8-azabicyclo [3.2.1]oct-3-yl)-2-methyl-1H-benzimidazole (**16**) was synthesized according to the method outlined below.



16



tert-butyl 4-(1-cyano-2-ethoxy-2-oxoethylidene)piperidine-1-carboxylate (**16a**)

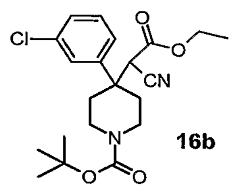


16a

A mixture of *tert*-butyl 4-oxo-1-piperidinecarboxylate (25.25 g, 127 mmol), ethyl cyanoacetate (13.8 ml, 130 mmol), ammonium acetate (2.73 g, 35.4 mmol), glacial acetic acid (6.3 ml) and benzene (250 ml) was heated for 4 hours at reflux under Dean Stark conditions. The reaction mixture was cooled to room temperature and washed successively with water, sodium bicarbonate solution and brine. Drying, filtration and evaporation of the organic phase provided *tert*-butyl 4-(1-cyano-2-ethoxy-2-oxoethylidene)piperidine-1-carboxylate as an oil that crystallized on standing (37 g, 99%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.28 (q, 2H, J = 7 Hz), 3.60 (br t,

2H, J = 6 Hz), 3.54 (br t, 2H, J = 6 Hz), 3.12 (t, 2H, J = 6 Hz), 2.76 (t, 2H, J = 6 Hz), 1.47 (s, 9H), and 1.35 (t, 3H, J = 7 Hz). ES-LCMS *m/z* 293 (M-1).

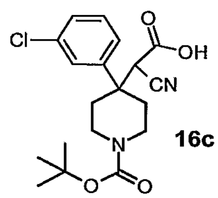
tert-butyl 4-(3-chlorophenyl)-4-(1-cyano-2-ethoxy-2-oxoethyl)piperidine-1-carboxylate **(16b)**



16b

A solution of 1-chloro-3-iodobenzene (14.1 g, 59.28 mmol) in diethyl ether (12 ml) was added dropwise to a mixture of magnesium turnings (1.59 g, 65.4 mmol) in diethyl ether (50 ml) at room temperature. When the Grignard reaction was complete, the resulting organomagnesium reagent was added dropwise to a stirred mixture of compound 16a (5.0 g, 17 mmol) and cuprous iodide (800 mg, 4.2 mmol) in tetrahydrofuran (30 mL) cooled to 0°C. The reaction mixture was stirred 1 hour at 0°C and then quenched with saturated ammonium chloride solution. Ethyl acetate (500 ml) was added and the mixture was washed successively with saturated ammonium chloride, water and brine. The organic layer was dried and concentrated and the resulting crude material was purified by column chromatography on silica gel eluting with 4:1 hexane:ethyl acetate. This afforded *tert*-butyl 4-(3-chlorophenyl)-4-(1-cyano-2-ethoxy-2-oxoethyl)piperidine-1-carboxylate (**16b**) as an oil (5.2 g, 75%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37-7.26 (m, 4H), 3.99 (br.q, 2H, J=6Hz), 3.91 (br m, 2H), 3.58 (s, 1H), 2.88 (br.m, 2H), 2.52 (ddd, 2H, J=6, 4, 3Hz), 2.04 (m, 2H), 1.43 (s, 9H), and 1.06 (t, 3H, J = 6 Hz). ES-LCMS *m/z* 429 (M+Na$^+$).

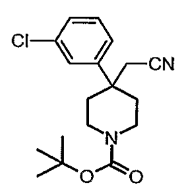
[1-(tert-butoxycarbonyl)-4-(3-chlorophenyl)piperidin-4-yl](cyano)acetic acid (16c)



16c

A solution of **16b** (5.2 g, 12.8 mmol) was dissolved in ethanol (30 ml) and 4 M aqueous sodium hydroxide (30 ml, 120 mmol) was added. The resulting solution was stirred at room temperature for 6.5 hours and then stored at 0°C overnight. Concentrated hydrochloric acid (10 ml) was added dropwise at 0°C and the mixture was then adjusted to pH~4 with 1 M hydrochloric acid. The solution was extracted with ethyl acetate (500 ml) and the aqueous phase was acidified to pH~3 and re-extracted with ethyl acetate. Both ethyl acetate layers were combined and washed with water and brine and then dried and concentrated to afford [1-(*tert*-butoxycarbonyl)-4-(3-chlorophenyl) piperidin-4-yl](cyano)acetic acid (**16c**) as a rigid foam (3.75 g, 77%). This material was used without further purification.

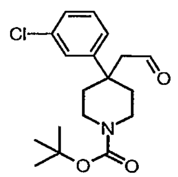
tert-butyl 4-(3-chlorophenyl)-4-(cyanomethyl) piperidine-1-carboxylate (16d)



16d

16d (3.75 g, 9.90 mmol) was dissolved in acetonitrile (30 ml) and cupric oxide (355 mg, 0.025 mmol) was added. This mixture was heated at reflux with stirring for 30 minutes and then cooled to room temperature and filtered through celite. Evaporation of the filtrate gave *tert*-butyl 4-(3-chlorophenyl)-4-(cyanomethyl)piperidine-1-carboxylate **16d** as an oil that crystallized on standing (3.0 g, 91%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37-7.27 (m, 4H), 3.74 (br.m, 2H), 3.08 (br.t, 2H, J=11Hz), 2.55 (s, 2H), 2.27 (br.dd, 2H, J = 11, 3Hz), 1.86 (ddd, 2H, J=14, 11, 4Hz), and 1.44 (s, 9H).

tert-butyl 4-(3-chlorophenyl)-4-(2-oxoethyl)piperidine-1-carboxylate (**16e**)

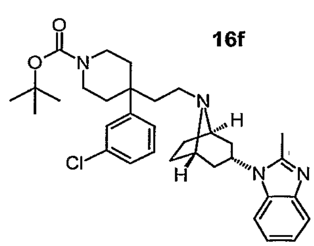


16e

A solution of **16d** (1.96 g, 5.85 mmol) in dichloromethane (25 mL) was cooled to -30°C and a 1M solution of diisobutyl aluminum hydride in dichloromethane (15.5 ml, 17.5 mmol) was added dropwise. During this addition the internal temperature was maintained at or below –35°C. When the addition was complete, the reaction mixture was stirred 30 min and then quenched at –35°C with methanol (0.7 ml) followed by saturated citric acid solution (50 ml). The mixture was allowed to warm to room temperature and then extracted with dichloromethane. Combined dichloromethane layers were dried, filtered and evaporated to provide *tert*-butyl 4-(3-chlorophenyl)-4-(2-oxoethyl)piperidine-1-carboxylate (**16e**) as an oil (1.3 g, 66%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.40 (t, 1H, J = 3 Hz), 7.34-7.22 (m, 4H), 3.61 (m, 2H), 3.26 (ddd, 2H, J=13, 9, 3Hz), 2.66 (d, 2H, J=3Hz), 2.19 (m, 2H), 1.86 (ddd, 2H, J=13, 9, 3Hz), and 1.44 (s, 9H). ^{13}C NMR (100MHz, $CDCl_3$): δ 201.4 (CH), 154.97 (C), 145.8 (C), 135.2 (C), 130.4 (CH), 127.3 (CH), 127.0 (CH), 124.9 (CH), 79.9 (C), 54.6 (2CH_2), 53.3 (C), 39.2 (CH_2), 35.5 (2CH_2), and 28.6 (3CH_3).

tert-butyl endo-4-(3-chlorophenyl)-4-{2-[3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidine-1-carboxylate (**16f**)

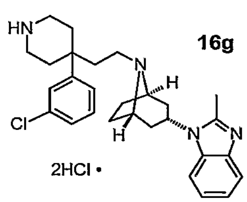
16f



Sodium triacetoxyborohydride (286 mg, 1.35 mmol) was added in one portion to a stirred mixture of 3-*endo*-1-(8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-

1*H*-benzimidazole dihydrochloride (compound IV, 250 mg, 0.90 mmol), **16e** (304 mg, 0.90 mmol), triethylamine (0.25 ml, 1.79 mmol) and powdered molecular sieves (250 mg) in dichloromethane (3 ml). After stirring 1 hour at room temperature, the reaction was quenched with saturated sodium bicarbonate solution and the dichloromethane layer was removed. The aqueous layer was extracted with dichloromethane and the combined organic layers were dried, filtered and concentrated to afford *tert*-butyl *endo*-4-(3-chlorophenyl)-4-{2-[3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidine-1-carboxylate as a rigid foam (500 mg, 99%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.47 (dd, 1H, J = 7, 2 Hz), 7.40 (br s, 1H), 7.39-7.35 (m, 3H), 7.27 (d, 1H, J = 7 Hz), 7.11 (dd, 1H, J = 7, 6 Hz), 7.08 (dd, 1H, J = 7, 6 Hz), 4.50 (m, 1H, J = 8 Hz), 3.48 (m, 2H); 3.24 (m, 2H), 3.11 (m, 2H), 2.48 (s, 3H), 2.35 (br dd, 2H, J = 15, 9 Hz), 1.98 (m , 2H), 1.90-1.70 (m, 10H), 1.59 (d, 2H, J = 8 Hz), and 1.36 (s, 9H). ES-LCMS *m/z* 585 (M+Na$^+$).

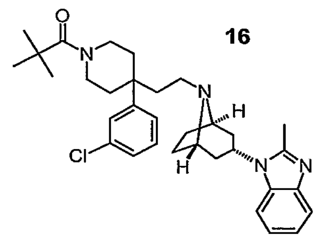
<u>endo-1-(8-{2-[4-(3-chlorophenyl) piperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1H-benzimidazole dihydrochloride (**16g**)</u>



16g

To a stirring solution of the product from example 16f (500 mg, 0.888 mmol) in dichloromethane (6 ml) was added a 4 M solution of hydrogen chloride in 1,4-dioxane (7 ml, 28 mmol). After stirring 15 minutes at room temperature, the supernatant was decanted. The remaining precipitate was triturated with ethyl acetate and dried under high vacuum to afford *endo*-1-(8-{2-[4-(3-chlorophenyl)piperidin-4-yl]ethyl}-8-azabicyclo [3.2.1]oct-3-yl)-2-methyl-1*H*-benzimidazole dihydrochloride (**16g**) as a pink solid (548 mg, 100%). This material was used without further purification. ES-LCMS *m/z* 463 (M+H).

endo-1-(8-{2-[4-(3-chlorophenyl)-1-(2,2-dimethylpropanoyl)piperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1H-benzimidazole (**16**)

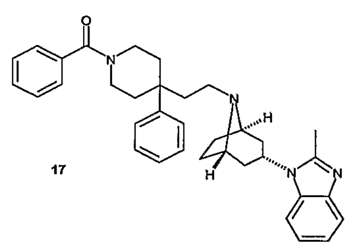


16

To a solution of **16g** (165 mg, 0.308 mmol) and triethylamine (0.086 ml, 0.616 mmol) in dichloromethane (3 ml) was added pivaloyl chloride (0.040 ml, 0.325 mmol). After stirring 1 hour at room temperature the reaction mixture was quenched with saturated sodium bicarbonate solution. The organic layer was separated, dried and concentrated. Purification of the resulting material by chromatography on silica gel eluting with 24:1 dichloromethane:methanol gave *endo*-1-(8-{2-[4-(3-chlorophenyl)-1-(2,2-dimethylpropanoyl)piperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1*H*-benzimidazole (**16**) as a rigid white foam (100 mg, 59%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.48 (d, 1H, J = 7 Hz), 7.42 (s, 1H), 7.41-7.34 (m, 3H), 7.28 (d, 1H, J = 7 Hz), 7.11 (br.t, 1H, J = 7 Hz), 7.08 (br.t, 1H, J = 7), 4.50 (m, 1H, J = 8 Hz), 3.73 (m, 2H), 3.29 (s, 3H), 3.25 (m, 4H), 2.35 (br.dd, 2H, J~22, 9 Hz), 2.02 (m 2H), 1.84-1.73 (m, 10H), 1.59 (d, 2H, J = 8 Hz), and 1.16 (s, 9H). ES-LCMS *m/z* 547 (M+H). HRMS $C_{33}H_{43}ClN_4O$ *m/z* 547.3186 $(M+H)_{Cal.}$ 547.3204 $(M+H)_{Obs.}$.

Example 17

1-{(1R,5S)-8-[2-(1-benzoyl-4-phenylpiperidin-4-yl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-2-methyl-1H-benzimidazole



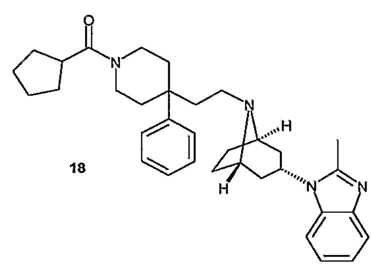
17

To a stirred solution of *endo* 2-methyl-1-{8-[2-(4-phenylpiperidin-4-yl)ethyl]-8-azabicyclo[3.2.1] oct-3-yl}-1H-benzimidazole dihydrochloride II

(0.53 g, 1.06 mmol) in dichloromethane (10 mL) and triethylamine (0.32 g, 3.18 mmol) was added benzoyl chloride (0.156g, 1.11 mmol) at 0 °C. The ice bath was then removed and the mixture allowed to stir for 30 min. The solvents were then removed in vacuo and the resulting solid was partitioned between ethyl acetate and water (3x). The organic layer was dried with magnesium sulfate and the solvent removed in vacuo, yielding crude **17**, which was them purified using the supercritical fluid chromatography, resulting in 525 mg of pure 1-{(1R,5S)-8-[2-(1-benzoyl-4-phenylpiperidin-4-yl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-2-methyl-1H-benzimidazole **17** (yield 93%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20 (1H, m), 6.94 (7H, m), 6.82 (4H, m), 6.70 (2H, m), 4.15 (1H, m), 3.75 (1H, m), 3.11 (1H, m), 2.98 (4H, m), 2,93 (1H, m), 2.78 (3H, m), 2.05 (3H, s), 2.04 (2H, m), 1.88 (3H, m), 1.70 (1H, m), 1.59–1.24 (4H, m), 1.14 (2H, m). HRMS m/z $(M+H)^+_{Calc}$ 533.3280; $(M+H)+_{Obs}$ 533.3300.

Example 18

1-((1R,5S)-8-{2-[1-(cyclopentylcarbonyl)-4-phenylpiperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1H-benzimidazole



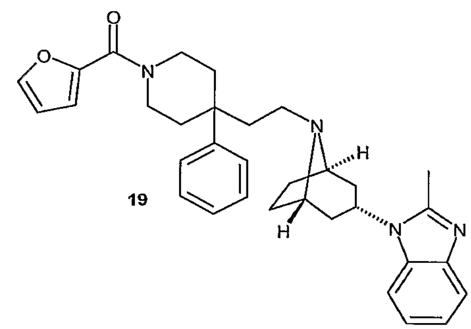
18

To a stirred solution of *endo* 2-methyl-1-{8-[2-(4-phenylpiperidin-4-yl)ethyl]-8-azabicyclo[3.2.1] oct-3-yl}-1H-benzimidazole dihydrochloride II (0.38 g, 0.75 mmol) in dichloromethane (7 mL) and triethylamine (0.227g, 2.25 mmol) was added cyclopentantane carbonyl chloride (0.104g, 0.79 mmol) at 0 °C. The ice bath was then removed and the mixture allowed to stir for 20 min. The solvents were then removed in vacuo and the solid partitioned between dichloroethane and water (3x), and the organic layer evaporated in vacuo resulting in 0.270 g of crude product. Following SFC

purification, 156 mg of the desired product 1-((1R,5S)-8-{2-[1-(cyclopentylcarbonyl)-4-phenylpiperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1H-benzimidazole (**18**). ^{1}H NMR (400 MHz, CD_3OD) δ 7.40 (1H, m), 7.25 (5H, m), 7.10 (3H, m), 4.52 (1H, m), 3.84 (1H, m), 3.63 (1H, m), 3.20-2.94 (4H, m), 2.86 (1H, m), 2.39 (3H, s), 2.10 (4H, m), 1.92-1.36 (20H, m). HRMS m/z $(M+H)^+_{Calc}$ 525.3606; $(M+H)^+_{Obs}$ 525.3593.

Example 19

1-((1R,5S)-8-{2-[1-(2-furoyl)-4-phenylpiperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1H-benzimidazole



19

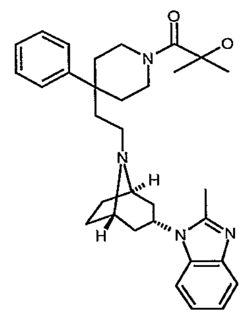
To a stirred solution of endo 2-methyl-1-{8-[2-(4-phenylpiperidin-4-yl)ethyl]-8-azabicyclo[3.2.1] oct-3-yl}-1H-benzimidazole dihydrochloride II (0.35 g, 0.69 mmol) in dichloromethane (7 mL) and triethylamine (0.209 g, 2.07 mmol) was added 2-furoyl chloride (0.094g, 0.72 mmol) at 0 °C. The ice bath was then removed and the mixture allowed to stir for 30 min. The solvents were then removed in vacuo and the solid was added ethyl acetate and water. The insoluble precipitate was then filtered off and subsequently characterized as the desired product **19**. Additional 0.18 g of the desired product **19** was obtained by extracting the organic layer with water (3x), drying with magnesium sulfate and evaporating solvents in vacuo. Following the SFC purification, on a portion of crude **19**, 60 mg of the desired product 1-((1R,5S)-8-{2-[1-(2-furoyl)-4-phenylpiperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1H-benzimidazole **19** was obtained (calculated yield 86%). ^{1}H NMR (400 MHz, CD_3OD) δ 7.57 (1H, dist. d, J=1.1Hz), 7.47 (1H, d, J=7.1 Hz), 7.43-7.29 (5H, m), 7.26-7.09 (3H, m), 6.89 (1H, d, J=3.6Hz), 6.48 (1H, dd,

J=1.8, 3.6Hz), 4.08 (2H, m), 3.84 (2H, m), 2.60 (5H, m), 2.42 (3H, s), 2.30 (2H, m), 2.20 (2H, m), 2.05 (7H, m), 1.83 (2H, m). HRMS m/z $(M+H)^+_{Calc}$ 523.3062; $(M+H)+_{Obs}$ 523.3073.

Example 20

2-methyl-1-(4-{2-[3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenyl-1-piperidinyl)-1-oxo-2-propanol

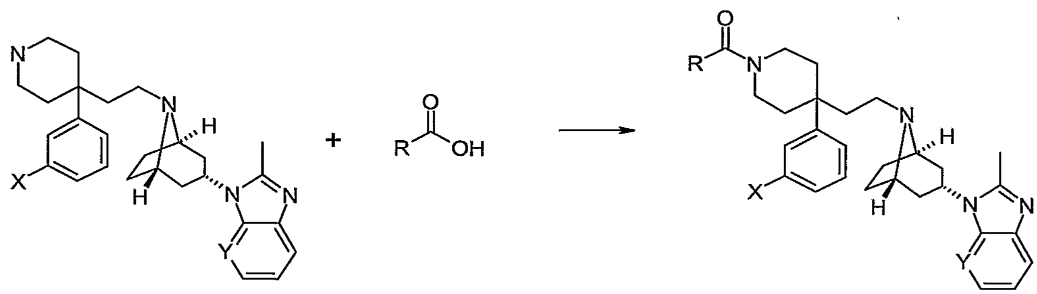
20



2-hydroxy-2-methylpropanoic acid (36 mg, 0.35 mmole) was dissolved in 0.92 ml of 1,2-dichloroethane. To this was added 1,1'-carbonyldiimidazole (37 mg, 0.23 mmole) and shaken for 30 min. 2-Methyl-1-{8-[2-(4-phenyl-4-piperidinyl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1H-benzimidazole (50 mg, 0.12 mmole)was added as a dry powder and shaking was resumed overnight. 1 ml of $NaHCO_3$ sat. was added to the reaction mixture and shaken, followed by filtration through a hydrophobic frit and concentrated to an oil. The oil was separated on silica using gradient flash chromatography (0-8% MeOH in $CHCl_3$) to afford 2-methyl-1-(4-{2-[3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenyl-1-piperidinyl)-1-oxo-2-propanol **20** 23.7 mg (38%) as a white glassy solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.7-7.6 (m, 1H), 7.1-7.4 (m, 8H), 4.7 (s, 1H), 4.0 (s, 2H), 3.2-3.4 (m, 4H), 2.6 (s, 3H), 2.2-2.5 (m, 5H), 2.1-1.7 (m, 11H), 1.7-1.5 (m, 2H).

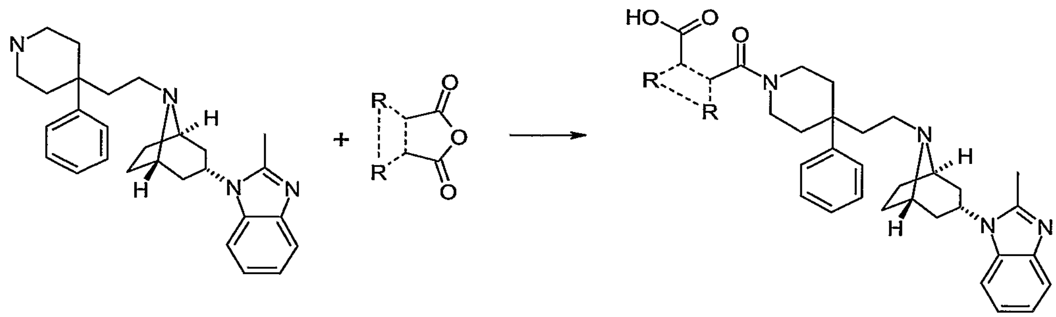
Selected coupling methods used in the synthesis of compoounds of formula I from II or IIa (Scheme I)

Method A (HATU)



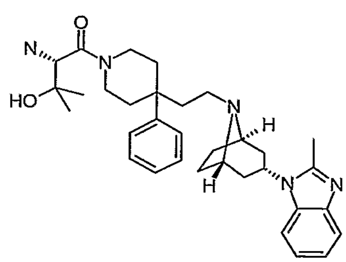
To 117 µmoles of each acid was added 117 µmoles (1 eq.) of amine-scaffold dissolved in 1 mL DMF and 351 µmoles (3 eq.) of DIPEA in 1 mL DMF at ambient temperature. After shaking 5 min to affect dissolution of materials, 117 µmoles (1 eq.) of HATU in 1 mL DMF was added and the reaction mixture and shaken at ambient temperature for 16 h. 351 µmoles of solid supported MP-Carbonate (Argonaut Technologies, Inc.) was added to the reaction mixture and shaken an additional 20h. The resin-bound carbonate was filtered off and the reaction mixture concentrated to dryness. The approximately 100 milligrams of impure compound was dissolved in 300 microliters of DMSO and brought up to a final volume of 500 microliters using methanol. This 500 microliter solution was injected by a Waters 2767 autosampler into an XTerra C18 5 micron particle HPLC column (19mmX150mm). Initial solvent flow was 20ml/min with 30% methanol and 70% water at a pH of 11 using ammonium hydroxide as buffer. Void volume was 2 minutes, and a linear gradient to 100% methanol in 10 minutes with a five minute wash at 100% methanol eluted the compound in approximately 10 minutes. A Micromass Platform LC mass spectrometer was used to monitor and split off the eluate for desired mass, and the purified fractions were collected using Micromass Fractionlynx software. Isolated compounds were characterized by LC-MS and ^{1}H NMR. Yields and representative data were included in the accompanying tables.

Method B (anhydride)



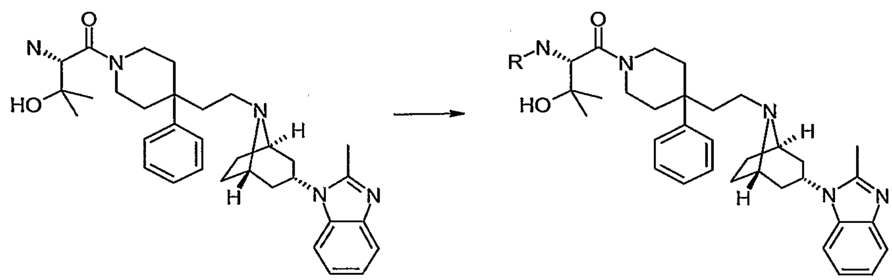
To 117 μmoles of the anhydride in 1 mL DCM was added 117 μmoles (1 eq.) of amine-scaffold dissolved in 1 mL DCM and stirred at ambient temperature for 1 h. In some cases, product crystalized from the reaction mixture and was isolated by filtration. Otherwise, the reaction mixture was concentrated and purified either by normal phase flash chromatography (SiO_2, $CHCl_3/CH_3OH$) or by reverse phase mass-directed HPLC as described in the Preparative HPLC Conditions A. Yields and representative data were included in the accompanying tables.

Method C – example of TFA-mediated Boc-deprotection -Example 21



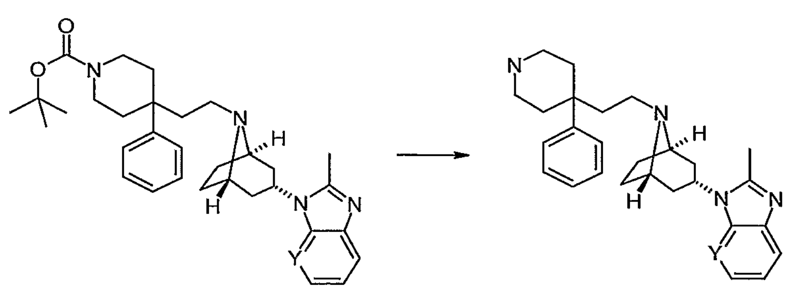
Boc-derivative (248 μmoles) was dissolved in 3 mL DCM and treated with 3 mL TFA for 40 min at ambient temperature. The reaction mixture was concentrated and pumped dry to give the TFA salt (example 21, mass 224 mg, Exact Mass = 543.3573) as a clear oil. Yield and representative data were included in the accompanying tables.

Method D – sulfonamide via sulfonyl chloride or amide via acyl chloride - Example 22 and Example 23



Product from example 21 (91 µmoles) was dissolved in 2 mL DCM and cooled to 0°C was treated with TEA (273 µmoles, 3 eq.) followed by either acetyl chloride or methanesulfonyl chloride (91 µmoles, 1 eq.). The reaction mixture was stirred 5 min at 0°C and then allowed to warm to ambient temperature and stirred an additional 30 min. The reaction mixture was diluted with 10 mL DCM, washed successively with saturated $NaHCO_3$ and brine, dried over $MgSO_4$, filtered, and concentrated to give the acetyl derivative (example 22) or methylsulfonyl (example 23), respectively. Products were purified by reverse phase mass-directed HPLC as described in Preparative HPLC Conditions A. Yields and representative data were included in the accompanying tables.

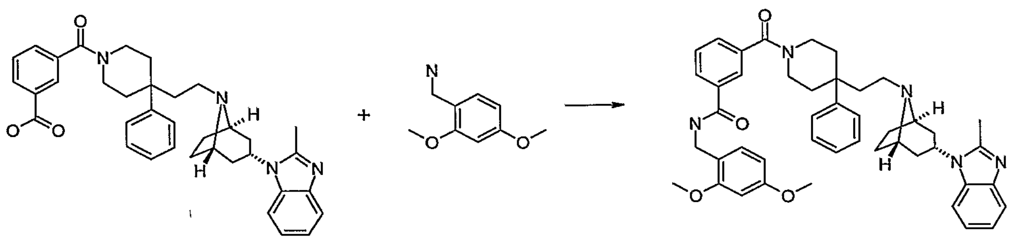
Method E – example of TFA-mediated Boc-deprotection



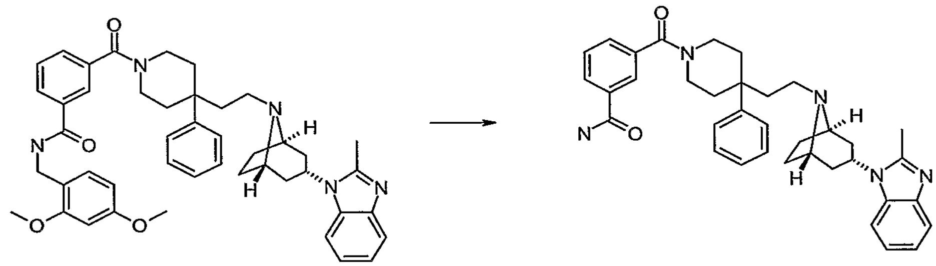
The Boc-protected amine (1.02 mmoles) was dissolved in 5 mL DCM and treated with 5 mL TFA at ambient temperature for 1 h. The reaction mixture was concentrated and treated with a biphasic mixture of EtOAc and saturated aqueous $NaHCO_3$. The mixture was stirred vigorously, and the solid filtered off and washed successively with water and EtOAc to give the

TFA salt of the amine. Yields and representative data were included in the accompanying tables.

Method F – HATU mediated formation of amides - Example 24

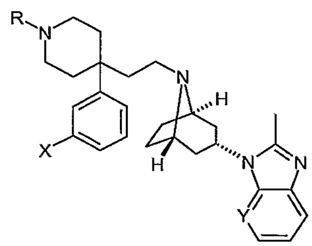


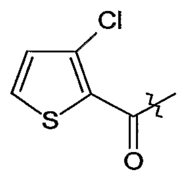
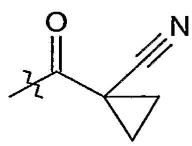
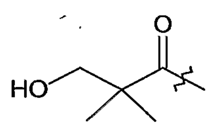
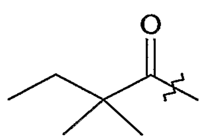
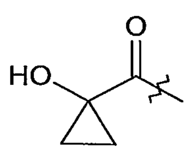
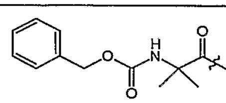
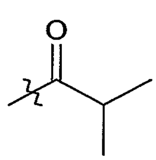
3-[(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]benzoic acid (259 mg, 449 μmoles) was combined with 2,4-dimethoxybenzylamine (449 μmoles, 1 eq.) in 3 mL DMF with DIPEA (449 μmoles, 1 eq.) and treated with HATU (449 μmoles, 1 eq.) at ambient temperature for 16 h. The reaction mixture was concentrated, dissolved in EtOAc, washed successively with saturated $NaHCO_3$ and brine, dried over $MgSO_4$, filtered, and concentrated. Products were purified by reverse phase HPLC as described in Preparative HPLC Conditions A to give the desired product. Yields and representative data were included in the accompanying tables.

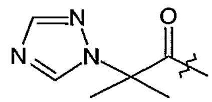
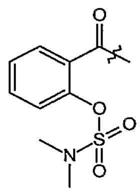
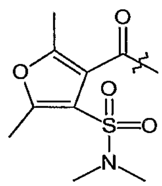
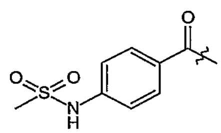
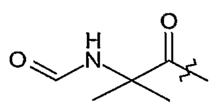
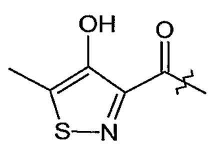
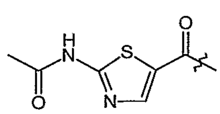
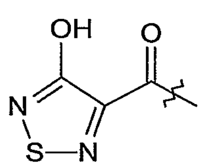
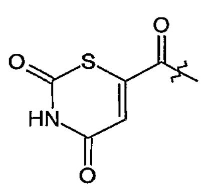


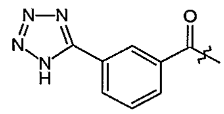
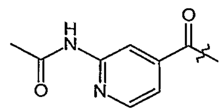
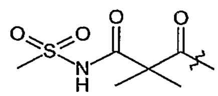
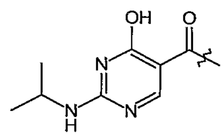
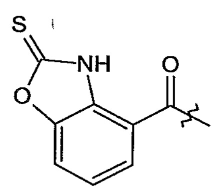
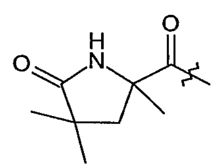
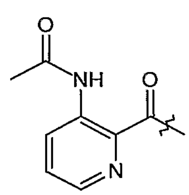
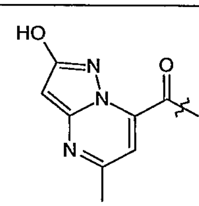
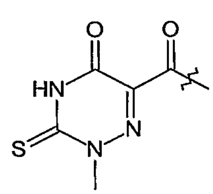
The product (73 mg, 101 μmoles) was dissolved in 3 mL DCM and treated with 3 mL TFA at ambient temperature for 24h. The reaction mixture was concentrated, dissolved in DCM, washed with saturated aqueous $NaHCO_3$, dried over $MgSO_4$, filtered and concentrated. The crude product was purified by normal phase flash chromatography (SiO_2, DCM/CH_3OH) to give the desired product.

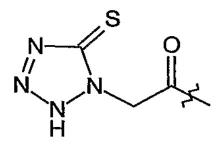
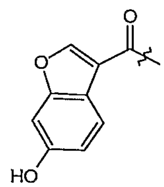
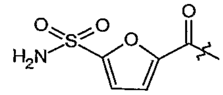
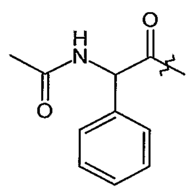
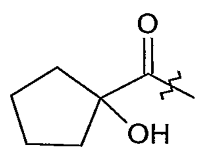
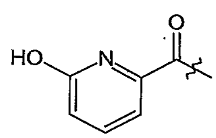
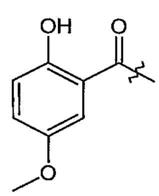
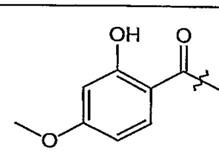
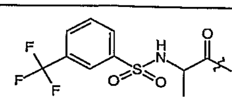
The accompanying tables list yields and representative data for compounds of the present invention.

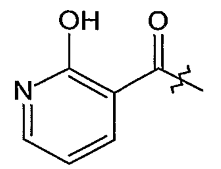
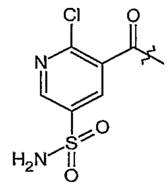
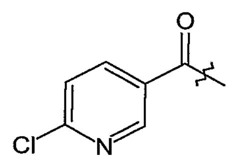
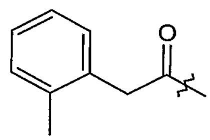
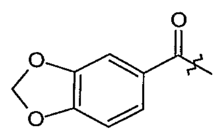
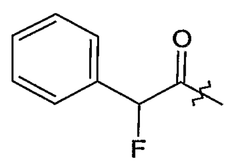
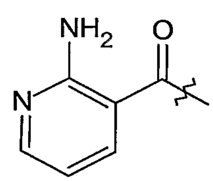
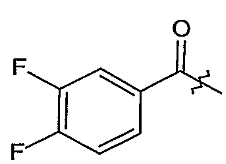


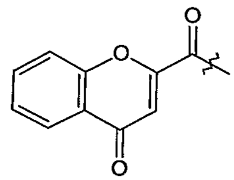
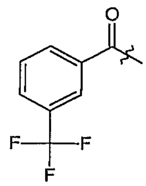
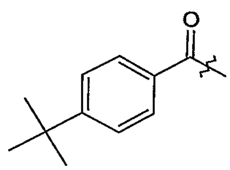
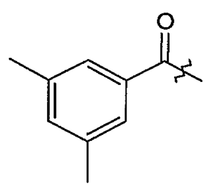
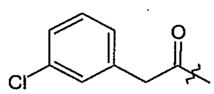
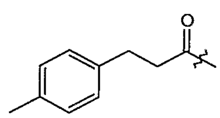
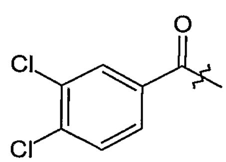
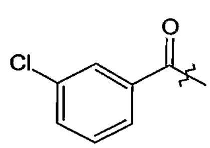
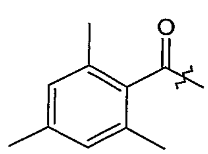
Example #	Acid # (for non-commercial compounds)	R	X	Y	% yield	LCMS result	ion	Acylation/coupling Method
25			H	C	53	573	(M+H)	Acid cloride
26			H	C		522	(M+H)	CDI
27			H	C		529	(M+H)	A
28			H	C		527	(M+H)	A
29			H	C		513	(M+H)	A
30			H	C		648	(M+H)	A
31			H	C		499	(M+H)	A

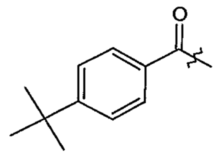
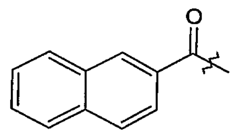
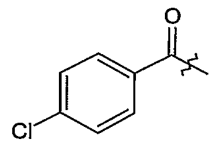
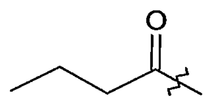
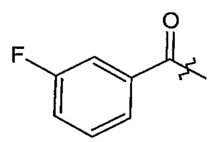
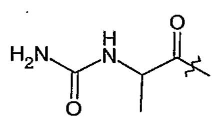
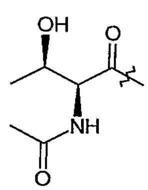
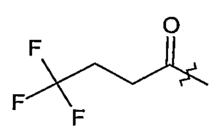
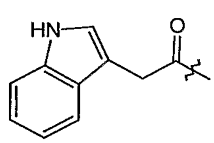
33			H	C		566	(M+H)	A
34			H	C	13	656	(M+H)	A
35			H	C	17	658	(M+H)	A
36			H	C	34	626	(M+H)	A
37			H	C	8	542	(M+H)	A
37			H	C	8	570	(M+H)	A
38			H	C	41	597	(M+H)	A
39			H	C	17	557	(M+H)	A
40			H	C	39	584	(M+H)	A

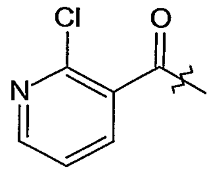
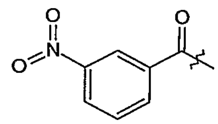
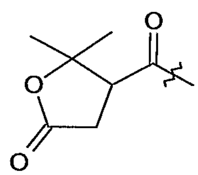
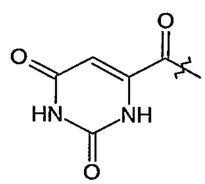
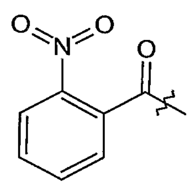
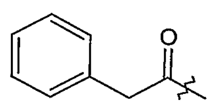
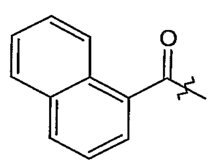
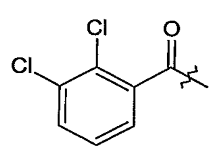
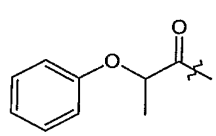
41			H	C	39	601	(M+H)	A
42			H	C	12	591	(M+H)	A
43			H	C		620	(M+H)	A
43			H	C	44	608	(M+H)	A
44			H	C	26	606	(M+H)	A
45			H	C	41	582	(M+H)	A
46			H	C	32	591	(M+H)	A
47			H	C	6	604	(M+H)	A
48			H	C	36	598	(M+H)	A

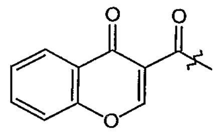
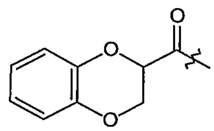
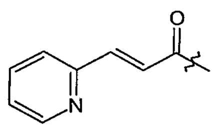
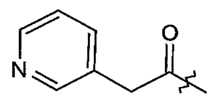
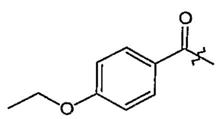
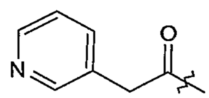
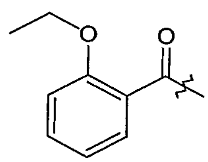
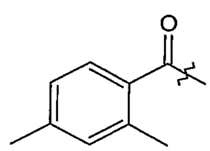
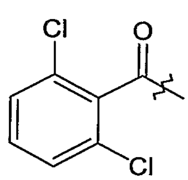
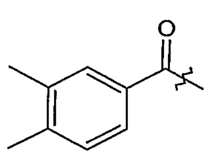
49			H	C	15	571	(M+H)	A	
50			H	C	19	589	(M+H)	A	
51			H	C	27	602	(M+H)	A	
52			H	C	40	604	(M+H)	A	
53			H	C	33	541	(M+H)	A	
54			H	C	46	550	(M+H)	A	
55			H	C	43	579	(M+H)	A	
56			H	C	48	579	(M+H)	A	
57			H	C	49	708	(M+H)	A	

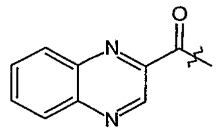
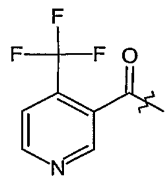
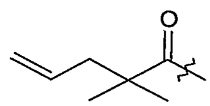
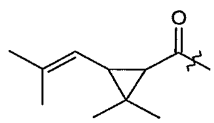
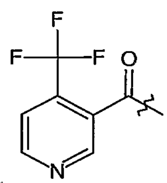
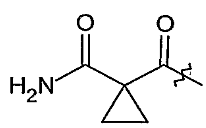
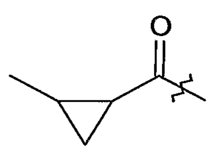
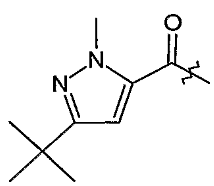
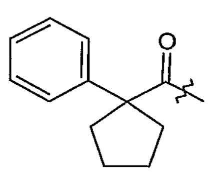
58			H	C	49	550	(M+H)	A
59			H	C		647	(M+H)	A
60			H	C	66	568	(M+H)	A
61			H	C	25	561	(M+H)	A
62			H	C	33	577	(M+H)	A
63			H	C	69	565	(M+H)	A
64			H	C	60	549	(M+H)	A
65			H	C	69	569	(M+H)	A

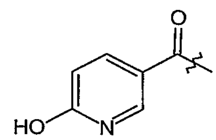
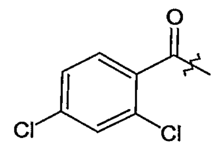
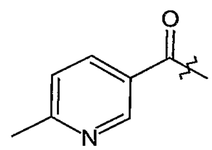
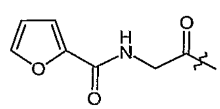
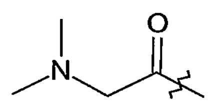
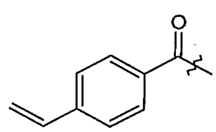
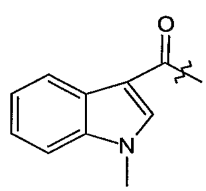
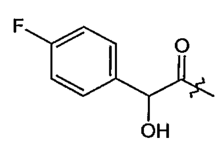
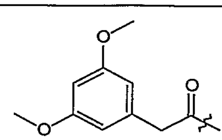
66			H	C	46	601	(M+H)	A
67			H	C	65	601	(M+H)	A
68			H	C	34	561	(M+H)	A
69			H	C	46	561	(M+H)	A
70			H	C	10	581	(M+H)	A
71			H	C	61	575	(M+H)	A
72			H	C	60	601	(M+H)	A
73			H	C	59	567	(M+H)	A
74			H	C	56	575	(M+H)	A

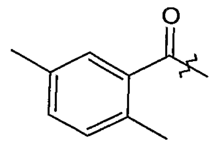
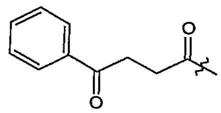
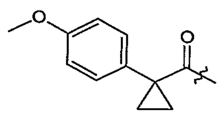
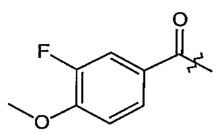
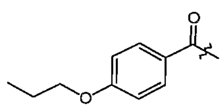
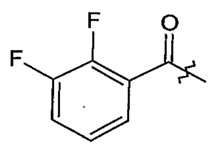
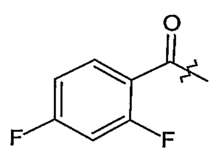
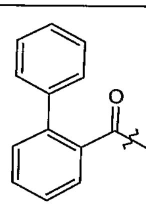
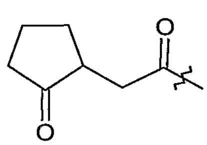
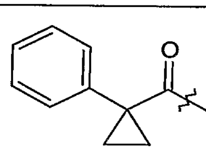
75			H	C	100	589	(M+H)	A
76			H	C	97	583	(M+H)	A
77			H	C	77	567	(M+H)	A
78			H	C	59	499	(M+H)	A
79			H	C	67	551	(M+H)	A
80			H	C	60	543	(M+H)	A
81			H	C	66	572	(M+H)	A
82			H	C	54	553	(M+H)	A
83			H	C	66	586	(M+H)	A

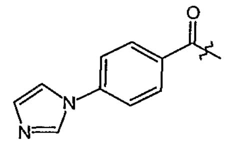
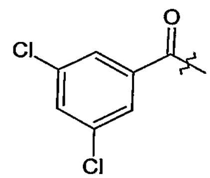
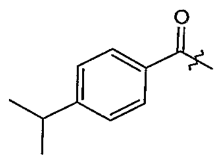
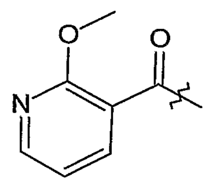
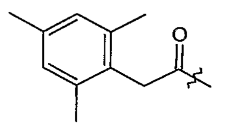
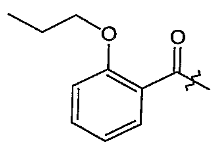
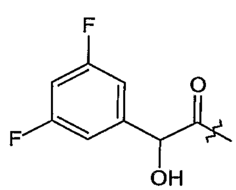
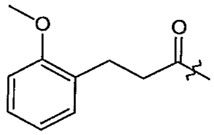
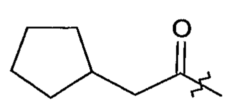
84			H	C	48	568	(M+H)	A
85			H	C	79	578	(M+H)	A
86			H	C	46	569	(M+H)	A
87			H	C	87	567	(M+H)	A
88			H	C	73	578	(M+H)	A
89			H	C	49	547	(M+H)	A
90			H	C	100	583	(M+H)	A
91			H	C	69	601	(M+H)	A
92			H	C	69	577	(M+H)	A

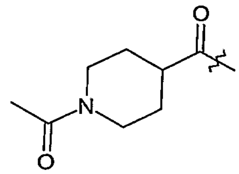
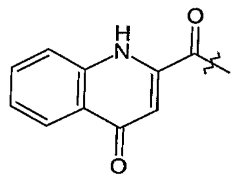
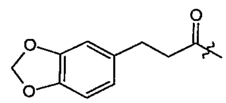
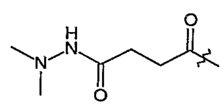
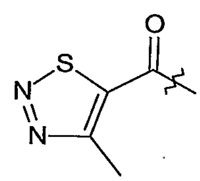
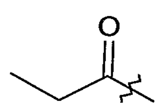
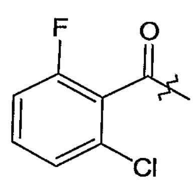
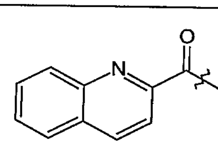
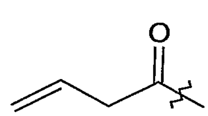
93			H	C	19	601	(M+H)	A
94			H	C	72	591	(M+H)	A
95			H	C	73	560	(M+H)	A
96			H	C	77	547	(M+H)	A
97			H	C	81	577	(M+H)	A
98			H	C	44	548	(M+H)	A
99			H	C	64	577	(M+H)	A
100			H	C	54	561	(M+H)	A
101			H	C	57	601	(M+H)	A
102			H	C	50	561	(M+H)	A

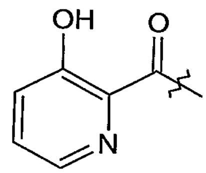
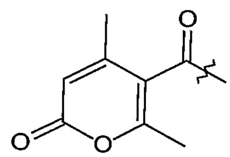
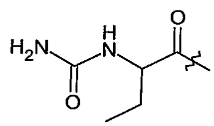
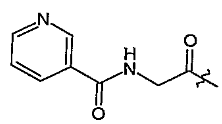
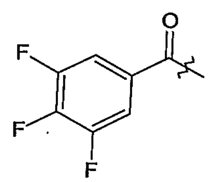
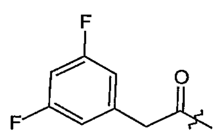
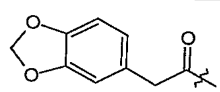
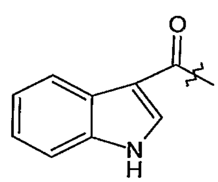
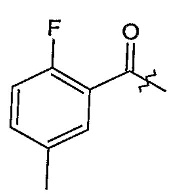
103			H	C	84	585	(M+H)	A
104			H	C	71	602	(M+H)	A
105			H	C	64	539	(M+H)	A
106			H	C	63	579	(M+H)	A
107			H	C	50	602	(M+H)	A
108			H	C	16	540	(M+H)	A
109			H	C	38	511	(M+H)	A
110			H	C	50	593	(M+H)	A
111			H	C	78	601	(M+H)	A

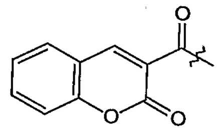
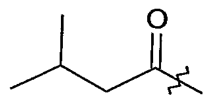
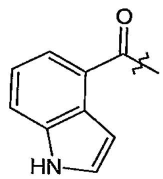
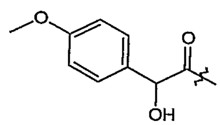
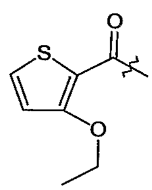
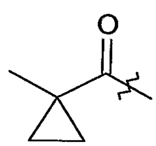
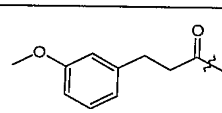
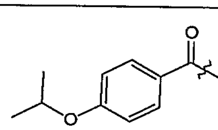
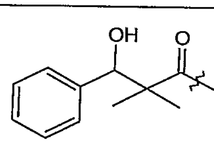
112			H	C	65	550	(M+H)	A
113			H	C	67	601	(M+H)	A
114			H	C	60	548	(M+H)	A
115			H	C	12	580	(M+H)	A
116			H	C	67	514	(M+H)	A
117			H	C	48	559	(M+H)	A
118			H	C	56	586	(M+H)	A
119			H	C	58	581	(M+H)	A
120			H	C	59	607	(M+H)	A

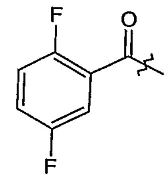
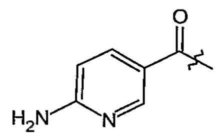
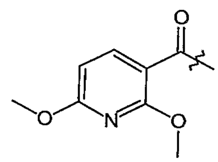
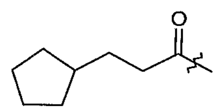
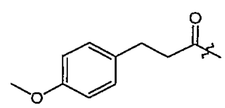
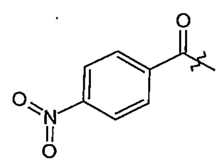
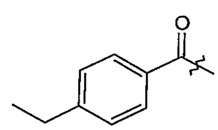
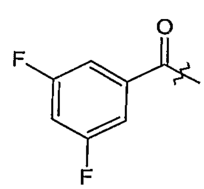
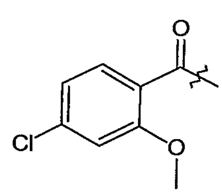
121			H	C	68	561	(M+H)	A
122			H	C	15	589	(M+H)	A
123			H	C	52	603	(M+H)	A
124			H	C	17	581	(M+H)	A
125			H	C	61	591	(M+H)	A
126			H	C	58	569	(M+H)	A
127			H	C	52	569	(M+H)	A
128			H	C	59	609	(M+H)	A
129			H	C	59	553	(M+H)	A
130			H	C	58	573	(M+H)	A

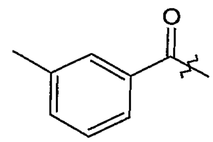
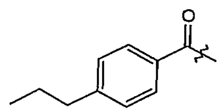
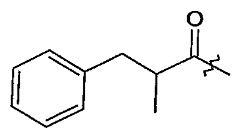
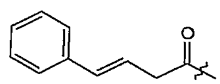
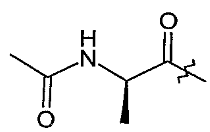
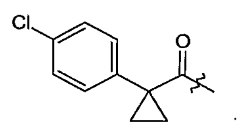
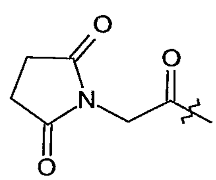
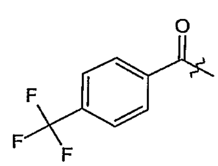
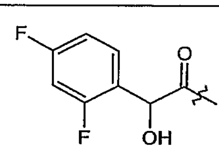
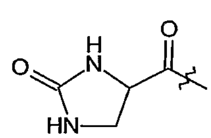
131			H	C	69	599	(M+H)	A
132			H	C	48	601	(M+H)	A
133			H	C	58	575	(M+H)	A
134			H	C	53	564	(M+H)	A
135			H	C	31	589	(M+H)	A
136			H	C	47	591	(M+H)	A
137			H	C	60	599	(M+H)	A
138			H	C	49	591	(M+H)	A
139			H	C	36	539	(M+H)	A

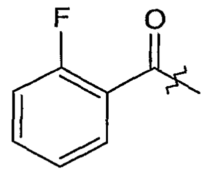
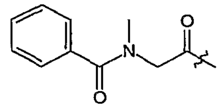
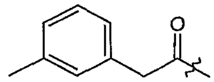
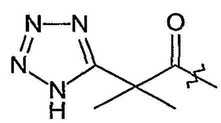
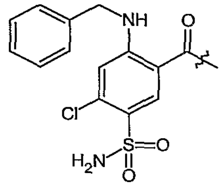
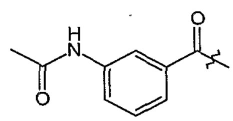
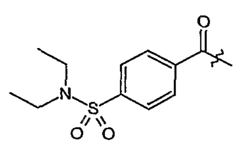
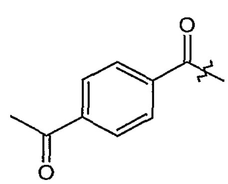
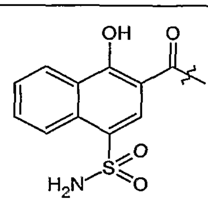
140			H	C	53	582	(M+H)	A	
141			H	C	48	600	(M+H)	A	
142			H	C	47	605	(M+H)	A	
143			H	C	48	571	(M+H)	A	
144			H	C	11	555	(M+H)	A	
145			H	C	27	485	(M+H)	A	
146			H	C	31	585	(M+H)	A	
147			H	C	47	584	(M+H)	A	
148			H	C	41	497	(M+H)	A	

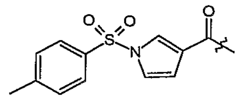
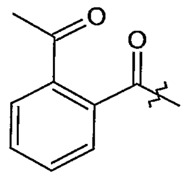
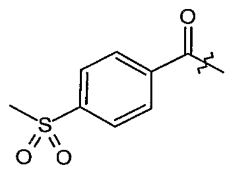
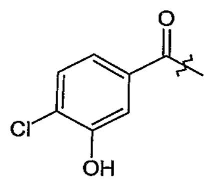
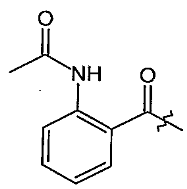
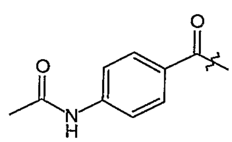
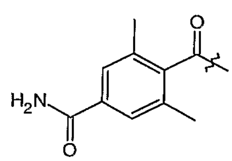
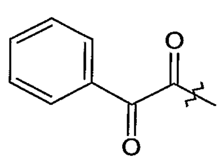
149			H	C	18	550	(M+H)	A
150			H	C	94	579	(M+H)	A
151			H	C	89	557	(M+H)	A
152			H	C	81	591	(M+H)	A
153			H	C	44	587	(M+H)	A
154			H	C	71	583	(M+H)	A
155			H	C	61	591	(M+H)	A
156			H	C	29	572	(M+H)	A
157			H	C	64	565	(M+H)	A

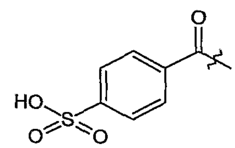
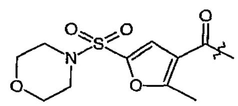
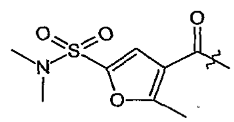
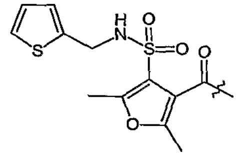
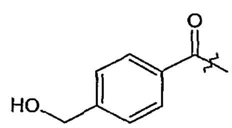
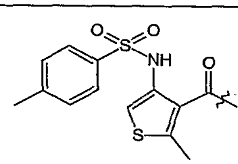
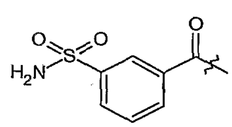
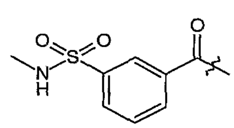
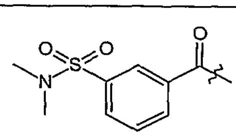
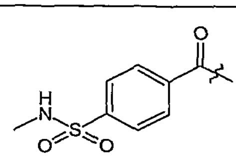
158			H	C	73	601	(M+H)	A
159			H	C	43	513	(M+H)	A
160			H	C	64	572	(M+H)	A
161			H	C	61	593	(M+H)	A
162			H	C	54	583	(M+H)	A
163			H	C	75	511	(M+H)	A
164			H	C	66	591	(M+H)	A
165			H	C	61	591	(M+H)	A
166			H	C	47	605	(M+H)	A

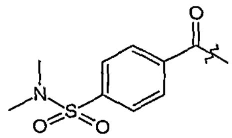
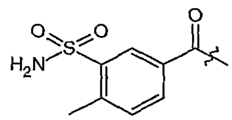
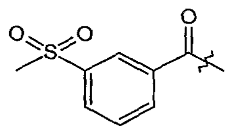
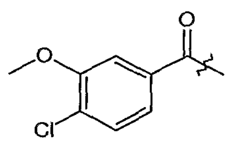
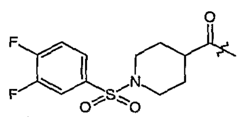
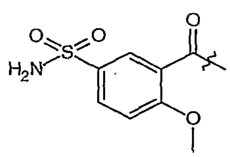
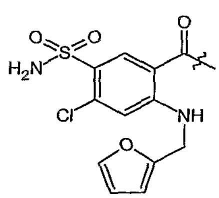
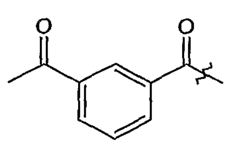
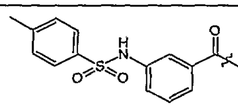
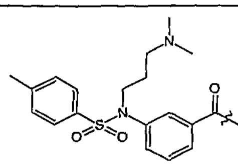
167			H	C	60	569	(M+H)	A
168			H	C	44	549	(M+H)	A
169			H	C	62	594	(M+H)	A
170			H	C	37	553	(M+H)	A
171			H	C	55	591	(M+H)	A
172			H	C	8	578	(M+H)	A
173			H	C	56	561	(M+H)	A
174			H	C	12	569	(M+H)	A
175			H	C	62	597	(M+H)	A

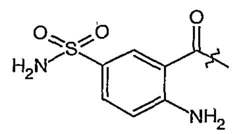
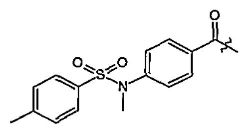
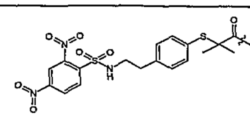
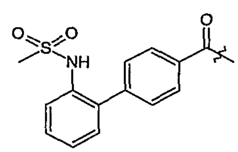
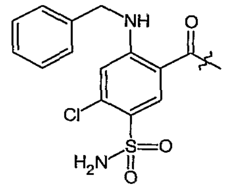
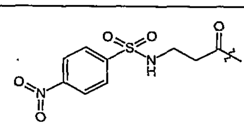
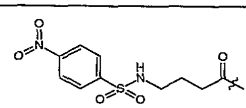
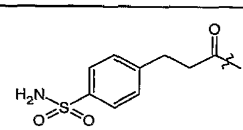
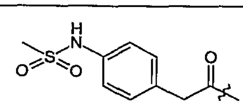
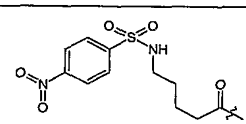
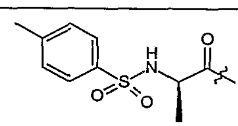
176			H	C	48	547	(M+H)	A
177			H	C	53	575	(M+H)	A
178			H	C	57	575	(M+H)	A
179			H	C	36	573	(M+H)	A
180			H	C	58	542	(M+H)	A
181			H	C	15	607	(M+H)	A
182			H	C	43	568	(M+H)	A
183			H	C	49	601	(M+H)	A
184			H	C	40	599	(M+H)	A
185			H	C	47	541	(M+H)	A

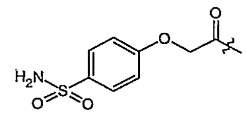
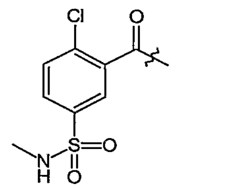
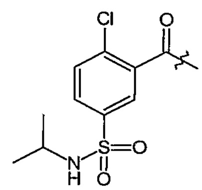
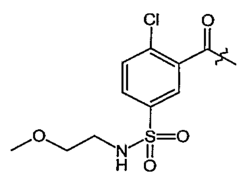
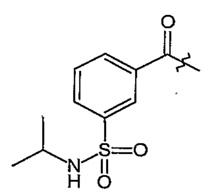
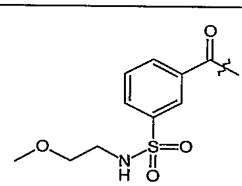
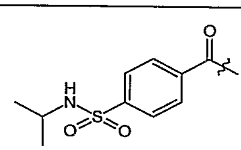
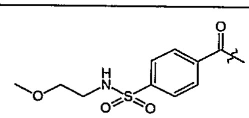
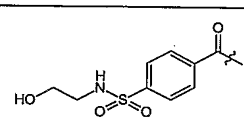
186			H	C	43	551	(M+H)	A
187			H	C	51	604	(M+H)	A
188			H	C	17	561	(M+H)	A
189			H	C	90	565.31	(M-1)	A
190			H	C	20	751.18	(M+H)	A
191			H	C	29	590.14	(M+H)	A
192			H	C	7	668.16	(M+H)	A
193			H	C	71	575.17	(M+H)	A
194			H	C	25	677.78	(M+H)	A

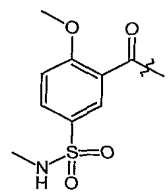
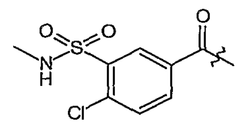
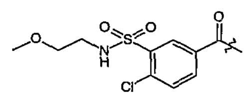
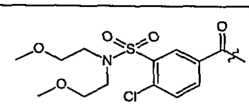
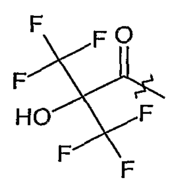
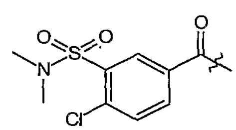
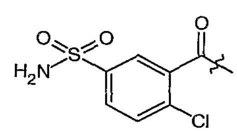
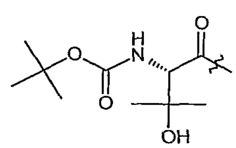
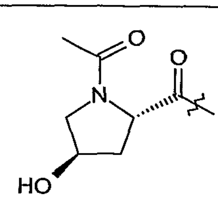
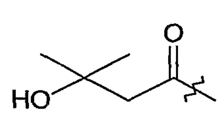
195			H	C	53	675.81	(M+H)	A
196			H	C	59	574.92	(M+H)	A
197			H	C	74	610.85	(M+H)	A
198			H	C	44	582.92	(M+H)	A
199			H	C	9	590.15	(M+H)	A
200			H	C	84	589.97	(M+H)	A
201			H	C	31	604.03	(M+H)	A
202			H	C	11	561.19	(M+H)	A

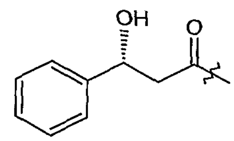
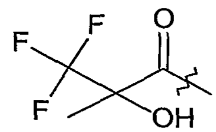
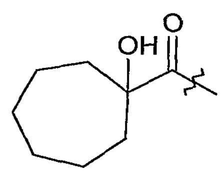
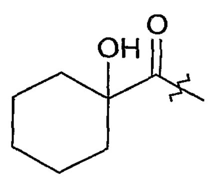
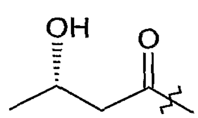
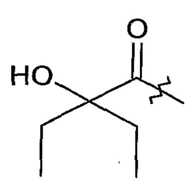
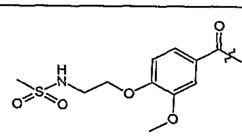
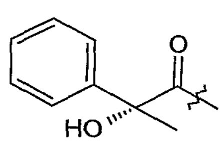
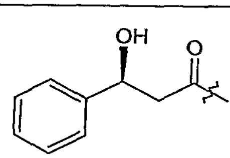
203			H	C	11	613.09	(M+H)	A
204			H	C	21	685.72	(M+H)	A
205			H	C	25	643.83	(M+H)	A
206			H	C	18	725.84	(M+H)	A
207			H	C	26	562.89	(M+H)	A
208			H	C	23	721.94	(M+H)	A
209			H	C	16	612.04	(M+H)	A
210			H	C	13	626.03	(M+H)	A
211			H	C	50	639.75	(M+H)	A
212			H	C	40	625.76	(M+H)	A

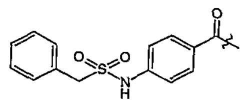
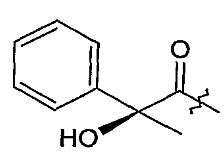
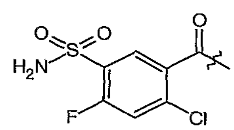
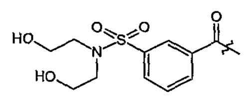
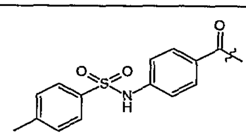
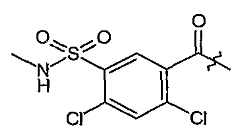
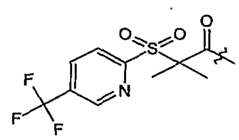
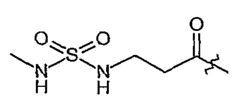
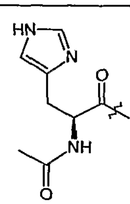
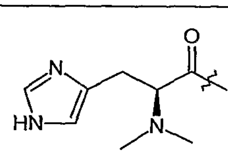
213			H	C	39	639.75	(M+H)	A
214			H	C	44	625.79	(M+H)	A
215			H	C	42	610.79	(M+H)	A
216			H	C	35	596.81	(M+H)	A
217			H	C	30	716.05	(M+H)	A
218			H	C	40	641.85	(M+H)	A
219			H	C	33	740.88	(M+H)	A
220			H	C	24	574.89	(M+H)	A
221			H	C	26	701.75	(M+H)	A
222			H	C	32	787.25	(M+H)	A

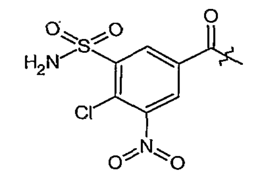
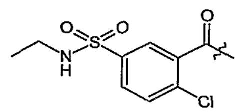
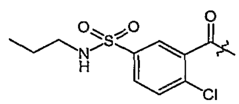
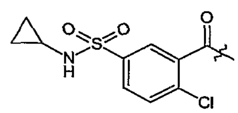
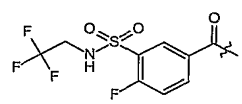
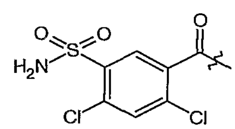
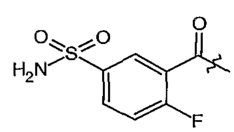
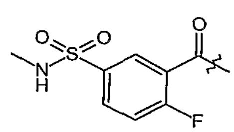
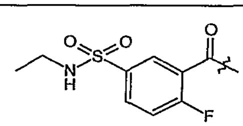
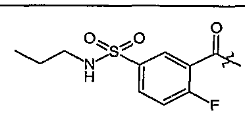
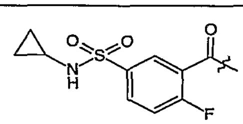
223			H	C	26	627.08	(M+H)	A
224			H	C	26	716.13	(M+H)	A
225			H	C	16	880.29	(M+H)	A
226			H	C	24	702.17	(M+H)	A
227			H	C	20	751.18	(M+H)	A
228			H	C	4	685.14	(M+H)	A
229			H	C	17	699.16	(M+H)	A
230			H	C	27	640.17	(M+H)	A
231			H	C	20	640.17	(M+H)	A
232			H	C	16	713.17	(M+H)	A
233			H	C	64	654.17	(M+H)	A

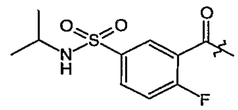
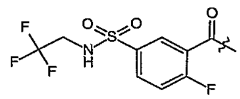
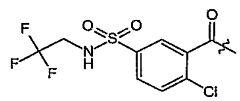
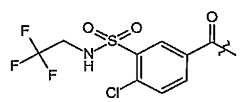
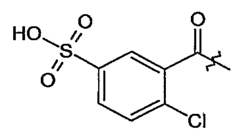
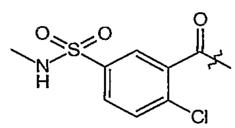
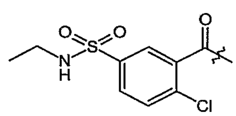
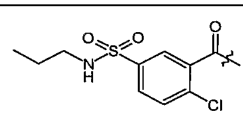
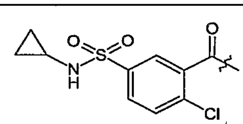
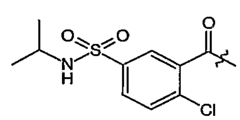
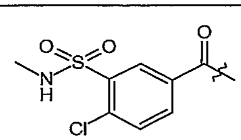
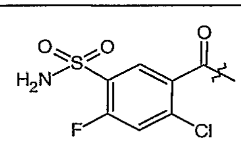
234			H	C	44	642.12	(M+H)	A
235	Acid 3		H	C	47	660.01	(M+H)	A
236	Acid 4		H	C	64	688.05	(M+H)	A
237	Acid 5		H	C	66	704.06	(M+H)	A
238	Acid 6		H	C	22	654.16	(M+H)	A
239	Acid 7		H	C	20	670.17	(M+H)	A
240	Acid 8		H	C	19	654.16	(M+H)	A
241	Acid 9		H	C	14	670.19	(M+H)	A
242	Acid 10		H	C	15	656.12	(M+H)	A

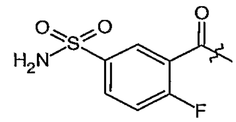
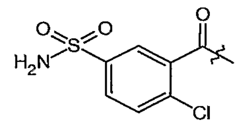
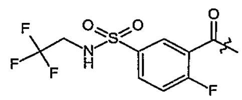
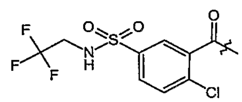
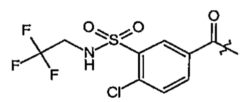
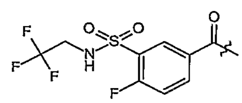
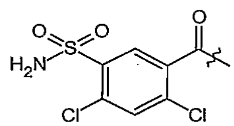
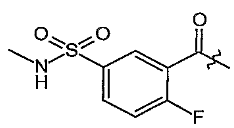
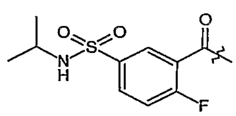
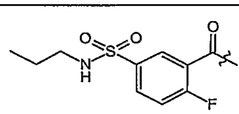
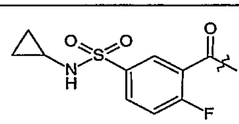
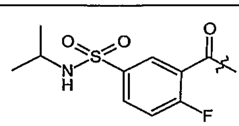
243	Acid 11		H	C	19	656.12	(M+H)	A
244	Acid 12		H	C	53	659.84	(M+H)	A
245	Acid 13		H	C	30	703.96	(M+H)	A
246	Acid 14		H	C	35	762.11	(M+H)	A
247			H	C	8	623.02	(M+H)	A
248	Acid 15		H	C	44	673.86	(M+H)	A
249	Acid 16		H	C	46	646.02	(M+H)	A
250	Acid 2		H	C	36	644.14	(M+H)	A
251			H	C	72	584.13	(M+H)	A
252			H	C	60	529.14	(M+H)	A

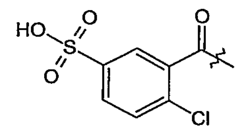
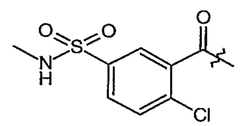
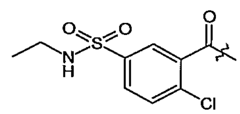
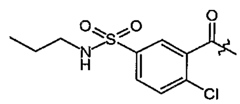
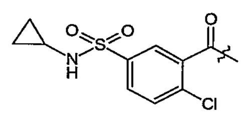
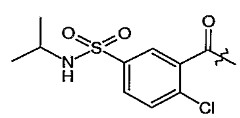
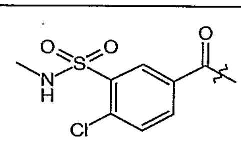
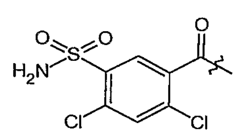
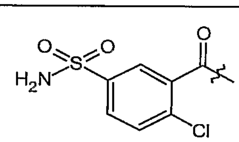
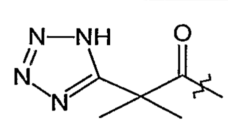
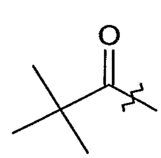
253			H	C	65	577.15	(M+H)	A
254			H	C	51	569.17	(M+H)	A
255			H	C	41	569.17	(M+H)	A
256			H	C	47	555.19	(M+H)	A
257			H	C	72	515.16	(M+H)	A
258			H	C	24	543.18	(M+H)	A
259			H	C	70	700.05	(M+H)	A
260			H	C	68	577.15	(M+H)	A
261			H	C	63	577.15	(M+H)	A

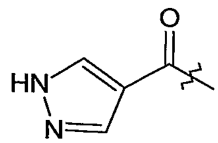
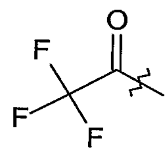
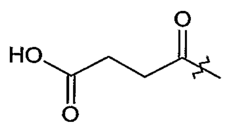
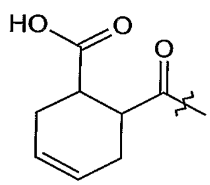
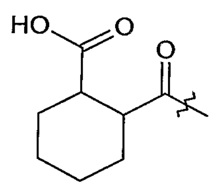
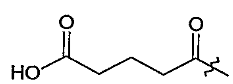
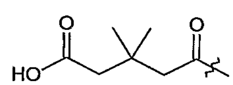
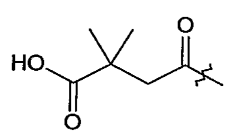
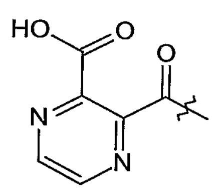
262			H	C	52	702.03	(M+H)	A
263			H	C	68	577.15	(M+H)	A
264			H	C	33	664.08	(M+H)	A
265			H	C	72	700.05	(M+H)	A
266			H	C	62	702.02	(M+H)	A
267	Acid 17		H	C	48	694.05	(M+H)	A
268			H	C	33	708.14	(M+H)	A
269			H	C	54	593.15	(M+H)	A
270			H	C	54	608.22	(M+H)	A
271			H	C	48	594.25	(M+H)	A

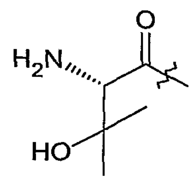
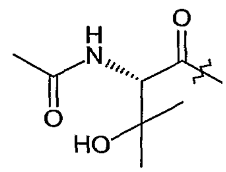
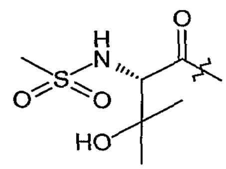
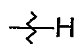
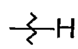
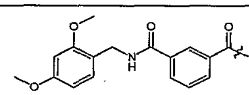
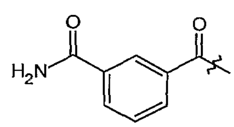
272			H	C	8	691.08	(M+H)	A
273	Acid 18		H	C	40	674.06	(M+H)	A
274	Acid 19		H	C	48	688.04	(M+H)	A
275	Acid 20		H	C	40	686.06	(M+H)	A
276	Acid 21		H	C	39	711.97	(M+H)	A
277			H	C	41	679.93	(M+H)	A
278	Acid 22		H	C	62	630.01	(M+H)	A
279	Acid 23		H	C	53	644.00	(M+H)	A
280	Acid 24		H	C	59	658.02	(M+H)	A
281	Acid 25		H	C	50	672.00	(M+H)	A
282	Acid 26		H	C	53	670.01	(M+H)	A

283	Acid 27		H	C	44	672.03	(M+H)	A
284	Acid 28		H	C	49	711.96	(M+H)	A
285	Acid 29		H	C	46	727.95	(M+H)	A
286	Acid 30		H	C	45	727.95	(M+H)	A
287			F	C	33	665.04	(M+H)	A
288	Acid 3		F	C	51	678.05	(M+H)	A
289	Acid 18		F	C	37	692.03	(M+H)	A
290	Acid 19		F	C	47	706.08	(M+H)	A
291	Acid 20		F	C	39	704.06	(M+H)	A
292	Acid 4		F	C	37	705.94	(M+H)	A
293	Acid 12		F	C	36	678.05	(M+H)	A
294			F	C	45	681.96	(M+H)	A

295	Acid 22		F	C	57	647.99	(M+H)	A
296			F	C	22	663.99	(M+H)	A
297	Acid 28		F	C	54	729.95	(M+H)	A
298	Acid 29		F	C	54	745.92	(M+H)	A
299	Acid 30		F	C	52	745.89	(M+H)	A
300	Acid 21		F	C	51	729.98	(M+H)	A
301			F	C	45	697.90	(M+H)	A
302	Acid 23		F	C	50	661.97	(M+H)	A
303	Acid 24		F	C	48	676.04	(M+H)	A
304	Acid 25		F	C	52	690.00	(M+H)	A
305	Acid 26		F	C	53	687.97	(M+H)	A
306	Acid 27		F	C	41	690.00	(M+H)	A

307			CH_3	C	28	661.06	(M+H)	A
308	Acid 3		CH_3	C	35	674.06	(M+H)	A
309	Acid 18		CH_3	C	46	688.04	(M+H)	A
310	Acid 19		CH_3	C	44	702.05	(M+H)	A
311	Acid 20		CH_3	C	42	700.07	(M+H)	A
312	Acid 4		CH_3	C	35	702.10	(M+H)	A
313	Acid 12		CH_3	C	45	674.06	(M+H)	A
314			CH_3	C	54	693.92	(M+H)	A
315			CH_3	C	47	659.97	(M+H)	A
316	Acid 1		H	N	44	567.92	(M+H)	A
317			H	N	37	513.93	(M+H)	A

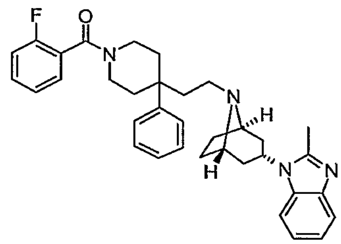
318			H	N	35	523.99	(M+H)	A
319			H	C	47	525.23	(M+H)	B
320			H	C	68	527.42	(M-1)	B
321			H	C	90	579.46	(M-1)	B
322			H	C	78	581.48	(M-1)	B
323			H	C	92	541.42	(M-1)	B
324			H	C	99	569.43	(M-1)	B
325			H	C	94	555.46	(M-1)	B
326			H	C	24	577.29	(M-1)	B

21			H	C	100	544.21	(M+H)	C
328			H	C	88	586.12	(M+H)	D
329			H	C	46	622.13	(M+H)	D
330			H	C	70	429.25	(M+H)	E
331			H	N	100	430.28	(M+H)	E
332			H	C	31	726.12	(M+H)	F
333			H	C	35	576.05	(M+H)	G

Proton NMR data for selected compounds from the above table:

Example 186

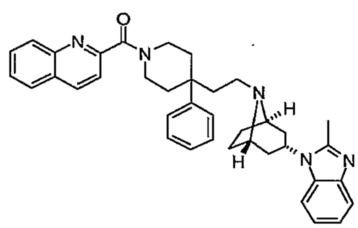
1-((1*R*,5*S*)-8-{2-[1-(2-fluorobenzoyl)-4-phenyl-4-piperidinyl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1*H*-benzimidazole



^{1}H NMR (400 MHz, Methanol-d4, ppm) δ 1.3 (m, 1H), 1.7 (m, 2H), 1.9 (m, 6H), 2.0 (m, 2H), 2.2 (m, 1H), 2.4 (m, 3H), 2.5 (s, 3H), 3.2 (m, 1H), 3.3 (m, 4H), 3.5 (m, 1H), 4.2 (m, 1H), 4.7 (m, 1H), 7.2 (m, 2H), 7.2 (m, 2H), 7.4 (m, 6H), 7.5 (m, 3 H).

Example 147

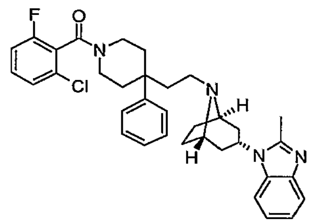
2-[(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenyl-1-piperidinyl)carbonyl]quinoline



^{1}H NMR (400 MHz, Methanol-d4, ppm) δ 1.9 (s, 1H), 2.3 (m, 2H), 2.6 (m, 9H), 2.9 (m, 1H), 3.1 (m, 3H), 3.2 (m, 2H), 3.9 (m, 5H), 4.2 (m, *J*=3.6Hz, 1H), 4.8 (m, 1H), 5.4 (m, 1H), 7.8 (m, 2H), 7.9 (m, 1H), 8.0 (m, 1H), 8.0 (m, *J*=8.2Hz, 1H), 8.1 (s, 5H), 8.1 (m, 3H), 8.1 (m, *J*=4.3, 2.5Hz, 1H), 8.2 (m, 1H).

Example 146

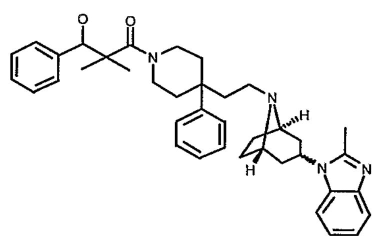
1-((1R,5S)-8-{2-[1-(2-chloro-6-fluorobenzoyl)-4-phenyl-4-piperidinyl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1H-benzimidazole



^{1}H NMR (400 MHz, Methanol-d4, ppm) δ 1.2 (m, 1H), 1.6 (m, 2H), 1.8 (m, 8H), 1.9 (m, 2H), 2.3 (m, 4H), 2.4 (m, 3H), 3.1 (m, 1H), 3.3 (m, 3H), 4.1 (m, 1H), 4.6 (m, 1H), 7.1 (m, 2H), 7.2 (m, 2H), 7.3 (m, 6H), 7.4 (m, 1H), 7.4 (m, 1H).

Example 166

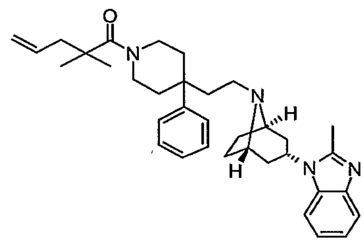
2,2-dimethyl-3-(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenyl-1-piperidinyl)-3-oxo-1-phenyl-1-propanol



^{1}H NMR (400 MHz, Methanol-d4, ppm) δ 1.8 (m, 3H), 1.9 (s, 3H), 2.3 (m, 3H), 2.5 (m, 5H), 2.7 (m, 4H), 3.0 (m, 2H), 3.1 (m, 3H), 3.2 (m, 3H), 4.0 (m, 5H), 4.7 (m, 2H), 5.4 (m, 1H), 7.8 (m, 2H), 7.9 (m, 2H), 7.9 (m, 1H), 8.0 (m, 1H), 8.1 (m, 6H), 8.2 (m, 2H).

Example 105

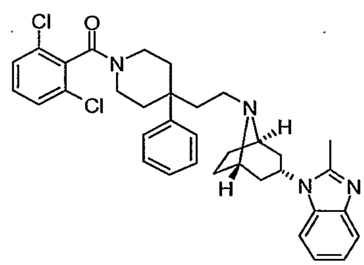
1-((1R,5S)-8-{2-[1-(2,2-dimethyl-4-pentenoyl)-4-phenyl-4-piperidinyl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1H-benzimidazole



^{1}H NMR (400 MHz, Methanol-d4, ppm) δ 0.6 (m, 1H), 0.9 (m, 1H), 1.5 (m, 1H), 1.7 (m, 3H), 1.9 (m, 9H), 2.3 (m, 2H), 2.4 (m, 4H), 2.5 (d, *J*=6.1Hz, 3H), 3.1 (m, 1H), 3.3 (m, 5H), 4.0 (m, 3H), 4.8 (m, 1H), 5.0 (m, 2H), 5.7 (m, 1H), 7.2 (m, 2H), 7.2 (m, 1H), 7.4 (m, 5H), 7.5 (m, 1H).

Example 101

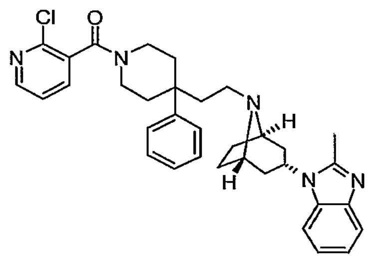
1-((1R,5S)-8-{2-[1-(2,6-dichlorobenzoyl)-4-phenyl-4-piperidinyl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1H-benzimidazole



^{1}H NMR (400 MHz, Methanol-d4, ppm) δ 1.2 (m, 1H), 1.6 (m, 2H), 1.8 (m, 6H), 1.9 (m, 2H), 2.2 (m, 1H), 2.3 (m, 3H), 2.4 (m, 3H), 3.1 (m, 1H), 3.3 (m, 5H), 4.1 (m, 1H), 4.7 (m, 1H), 7.1 (m, 2H), 7.2 (m, 1H), 7.3 (m, 5H), 7.4 (m, 2H), 7.4 (m, 1H), 7.4 (m, 1H).

Example 84

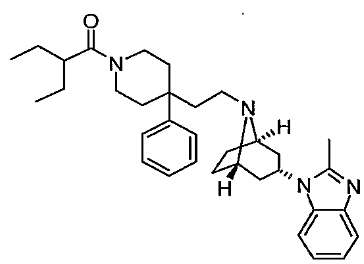
1-[(1R,5S)-8-(2-{1-[(2-chloro-3-pyridinyl)carbonyl]-4-phenyl-4-piperidinyl}ethyl)-8-azabicyclo[3.2.1]oct-3-yl]-2-methyl-1H-benzimidazole



^{1}H NMR (400 MHz, Methanol-d4, ppm) δ 1.6 (d, *J*=7.5Hz, 2H), 1.9 (m, 9H), 2.2 (d, *J*=15.7Hz, 1H), 2.4 (m, 3H), 2.5 (m, 3H), 3.1 (m, 1H), 3.3 (m, 5H), 4.1 (dd, *J*=9.3, 4.3Hz, 1H), 4.7 (m, 1H), 7.1 (m, 2H), 7.2 (m, 1H), 7.3 (m, 5H), 7.4 (m, 2H), 7.8 (m, 1H), 8.4 (m, 1H).

Example 334

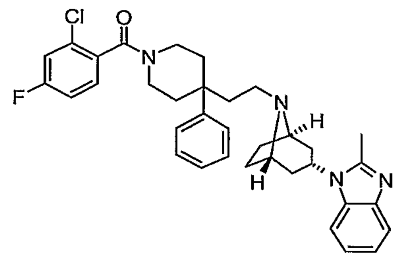
1-((1R,5S)-8-{2-[1-(2-ethylbutanoyl)-4-phenyl-4-piperidinyl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1H-benzimidazole



^{1}H NMR (400 MHz, Methanol-d4, ppm) δ 1.4 (t, *J*=7.5Hz, 3H), 1.6 (t, *J*=7.5Hz, 3H), 1.9 (m, 1H), 2.2 (m, 6H), 2.5 (m, 9H), 2.9 (m, 2H), 3.1 (m, 2H), 3.2 (d, *J*=6.4Hz, 3H), 3.4 (m, 1H), 3.9 (m, 1H), 4.0 (none, 2H), 4.0 (m, 1H), 4.5 (m, 1H), 4.7 (m, 1H), 5.4 (m, 1H), 7.8 (m, 2H), 7.9 (m, 1H), 8.1 (m, 5H), 8.2 (m, 1H).

Example 335

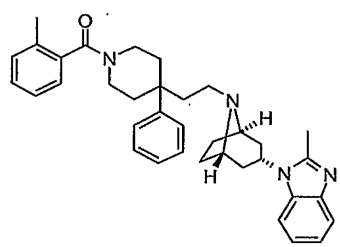
1-((1R,5S)-8-{2-[1-(2-ethylbutanoyl)-4-phenyl-4-piperidinyl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1H-benzimidazole



^{1}H NMR (400 MHz, Methanol-d4, ppm) δ 1.2 (s, 1H), 1.6 (m, 2H), 1.8 (m, 9H), 2.2 (m, 1H), 2.3 (m, 3H), 2.4 (m, 3H), 3.1 (m, 1H), 3.3 (m, 4H), 4.1 (m, 1H), 4.7 (m, 1H), 7.1 (m, 2H), 7.2 (m, 2H), 7.3 (m, 1H), 7.3 (m, 5H), 7.4 (dd, *J*=8.6, 6.1Hz, 1H), 7.4 (m, 1H).

Example 336

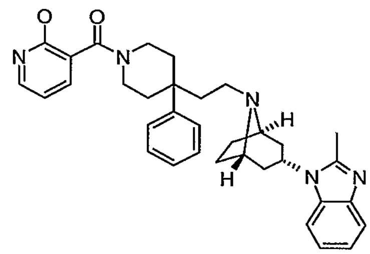
2-methyl-1-((1R,5S)-8-{2-[1-(2-methylbenzoyl)-4-phenyl-4-piperidinyl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-1H-benzimidazole



^{1}H NMR (400 MHz, Methanol-d4, ppm) δ 1.2 (m, 1H), 1.6 (m, 2H), 1.7 (m, 1H), 1.9 (m, 8H), 2.1 (m, 2H), 2.3 (m, 4H), 2.4 (m, 3H), 3.1 (m, 1H), 3.3 (m, 5H), 4.1 (m, 1H), 4.6 (m, 1H), 7.1 (m, 7H), 7.3 (m, 5H), 7.4 (m, 1H).

Example 337

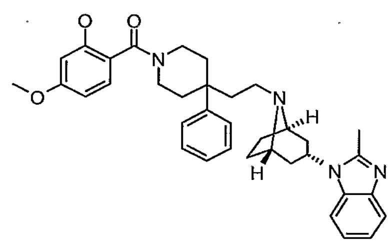
3-[(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenyl-1-piperidinyl)carbonyl]-2-pyridinol



^{1}H NMR (400 MHz, DMSO-d6) δ ppm 1.5 (m, 2H), 1.8 (m, 9H), 2.0 (m, 2H), 2.3 (m, 3H), 2.4 (s, 3H), 3.2 (d, *J*=6.4Hz, 4H), 3.7 (s, 2H), 4.5 (m, 1H), 6.4 (m, 2H), 7.0 (d, *J*=8.6Hz, 1H), 7.1 (m, 2H), 7.2 (m, 1H), 7.3 (m, 5H), 7.4 (m, 1H), 9.8 (s, 1H).

Example 338

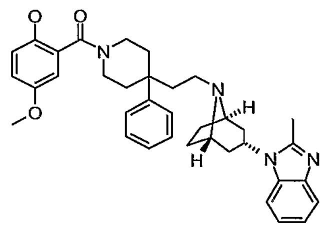
5-methoxy-2-[(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenyl-1-piperidinyl)carbonyl]phenol



^{1}H NMR (400 MHz, DMSO-d6) δ ppm 1.5 (m, 2H), 1.8 (m, 8H), 2.1 (m, 2H), 2.3 (m, 2H), 2.4 (m, 3H), 2.4 (m, 1H), 3.2 (d, *J*=7.1Hz, 3H), 3.3 (s, 3H), 3.6 (m, 2H), 3.7 (s, 2H), 4.5 (m, 1H), 6.4 (m, 2H), 7.0 (d, *J*=8.2Hz, 1H), 7.1 (m, 2H), 7.2 (m, 1H), 7.3 (m, 5H), 7.4 (m, 1H), 9.8 (s, 1H).

Example 339

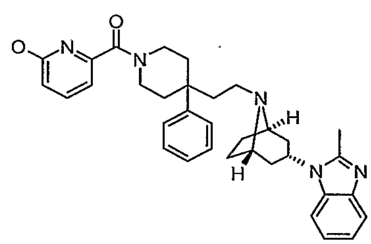
4-methoxy-2-[(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenyl-1-piperidinyl)carbonyl]phenol



^{1}H NMR (400 MHz, DMSO-d6) δ ppm 1.5 (m, 2H), 1.8 (m, 9H), 2.0 (m, 2H), 2.3 (m, 2H), 2.4 (m, 3H), 2.5 (m, 1H), 3.2 (m, 6H), 3.6 (s, 2H), 3.8 (m, 1H), 4.4 (m, 1H), 6.6 (d, *J*=2.9Hz, 1H), 6.7 (d, *J*=8.6Hz, 1H), 6.8 (m, 1H), 7.1 (m, 2H), 7.2 (m, 1H), 7.3 (m, 5H), 7.4 (dd, *J*=8.2, 6.4Hz, 1H), 9.2 (s, 1H).

Example 340

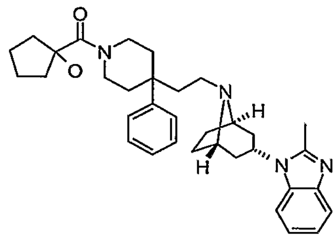
6-[(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenyl-1-piperidinyl)carbonyl]-2-pyridinol



^{1}H NMR (400 MHz, DMSO-d6) δ ppm 1.5 (m, 2H), 1.8 (m, 8H), 2.1 (m, 2H), 2.3 (m, 2H), 2.4 (m, 3H), 2.5 (m, 1H), 3.3 (m, 7H), 3.8 (s, 1H), 4.5 (m, 1H), 6.3 (d, *J*=6.4Hz, 1H), 6.4 (d, *J*=9.3Hz, 1H), 7.1 (m, 2H), 7.2 (m, 1H), 7.3 (m, 5H), 7.4 (m, 2H).

Example 341

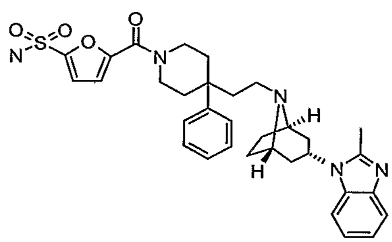
1-[(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenyl-1-piperidinyl)carbonyl]cyclopentanol



^{1}H NMR (400 MHz, DMSO-d6) δ ppm 1.7 (m, 15H), 2.0 (m, 3H), 2.3 (m, 2H), 2.4 (m, 4H), 2.5 (m, 1H), 2.7 (m, 1H), 3.2 (m, 7H), 3.8 (d, *J*=109.2Hz, 1H), 4.5 (m, 1H), 7.1 (m, 2H), 7.1 (m, 1H), 7.3 (m, 5H), 7.4 (m, *J*=7.1Hz, 1H).

Example 51

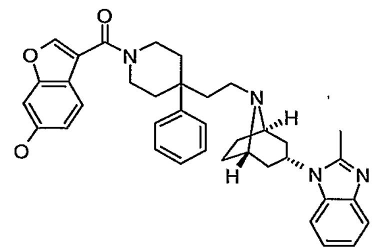
5-[(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenyl-1-piperidinyl)carbonyl]-2-furansulfonamide



^{1}H NMR (400 MHz, DMSO-d6) δ ppm 1.2 (s, 1H), 1.5 (m, 2H), 1.8 (m, 8H), 2.1 (m, 1H), 2.3 (m, 2H), 2.4 (s, 3H), 2.5 (m, 3H), 3.2 (m, 2H), 3.2 (m, 1H), 3.4 (m, 2H), 3.8 (m, 2H), 4.5 (m, 1H), 7.1 (m, 2H), 7.2 (t, *J*=7.0Hz, 1H), 7.3 (m, 5H), 7.4 (m, 1H).

Example 50

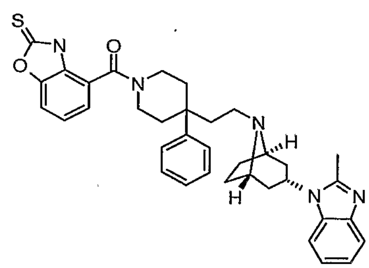
3-[(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenyl-1-piperidinyl)carbonyl]-1-benzofuran-6-ol



^{1}H NMR (400 MHz, DMSO-d6) δ ppm 1.5 (m, 2H), 1.7 (m, 9H), 2.1 (d, *J*=5.7Hz, 2H), 2.3 (m, 2H), 2.4 (s, 3H), 2.5 (m, 2H), 2.5 (m, 1H), 3.2 (m, 2H), 3.3 (m, 1H), 3.7 (m, 2H), 4.5 (m, 1H), 6.8 (dd, *J*=8.6, 2.1Hz, 1H), 6.9 (d, *J*=1.8Hz, 1H), 7.1 (m, 2H), 7.2 (t, *J*=7.0Hz, 1H), 7.3 (m, 6H), 7.4 (m, 1H), 8.0 (s, 1H).

Example 44

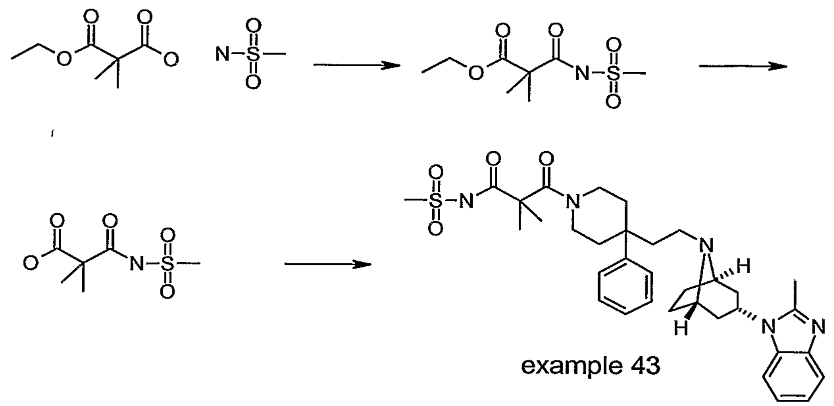
4-[(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenyl-1-piperidinyl)carbonyl]-1,3-benzoxazole-2(3H)-thione



^{1}H NMR (400 MHz, DMSO-d6) δ ppm 1.7 (s, 3H), 1.9 (m, 7H), 2.0 (m, 3H), 2.2 (m, 1H), 2.4 (m, 5H), 2.5 (m, 2H), 3.1 (m, 2H), 3.4 (m, 2H), 3.9 (m, 1H), 4.6 (m, 1H), 7.1 (m, 4H), 7.2 (m, 1H), 7.3 (m, 6H), 7.4 (m, 1H).

Example 43

N-[2,2-dimethyl-3-(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenyl-1-piperidinyl)-3-oxopropanoyl]methane sulfonamide



3-Ethoxy-2,2-dimethyl-3-oxopropanoic acid (100 mg, 0.624 mmole) was added to a stirring suspension of 2.5 equivalents of PS-DCC from Argonaut and 3 equivalents of dimethylaminopyridine in DCM. To this was added methanesulfonamide (41.6 mg, 0.437 mmole). The solution was filtered of and concentrated to give 69.3 mg of ethyl 2,2-dimethyl-3-[(methy-lsulfonyl)amino]-3-oxopropanoate (67% yield crude). MS ES- 236 (M-H). ^{1}H NMR (300 MHz, Chloroform-d) δ ppm 1.4 (t, *J*=6.7Hz, 3H), 1.6 (s, 6H), 3.3 (m, 3H), 4.3 (m, 2H).

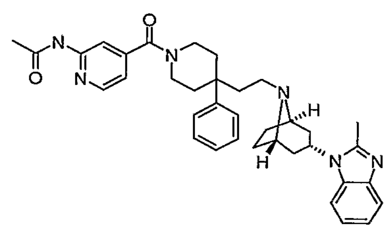
Ethyl 2,2-dimethyl-3-[(methylsulfonyl)amino]-3-oxopropanoate was hydrolyzed without purification in 2 ml of 1,4-dioxane and 2 ml of 1M LiOH at 45 °C. The solvent was removed under vacuum and the residue 2,2-dimethyl-*N*-(methylsulfonyl)-3-oxo-alanine was used in the next step without further purification. MS ES- 209 (M-H) 1H NMR (400 MHz, methanol-d4) δ ppm 1.4 (s, 6H) and 3.2 (s, 3H).

Example 43

N-[2,2-dimethyl-3-(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenyl-1-piperidinyl)-3-oxopropanoyl] methanesulfonamide was made using the HATU coupling method A. MS ES+ 620 (M+H). ^{1}H NMR (300 MHz, methanol-d4) δ ppm 1.4 (m, 4H), 1.9 (s, 2H), 2.2 (m, 2H), 2.3 (s, 4H), 2.4 (m, 2H), 2.8 (m, 2H), 2.8 (s, 3H), 2.9 (m, 2H), 3.2 (d, J=7.5Hz, 2H), 3.3 (m, 2H), 3.5 (s, 1H), 4.1 (d, J=8.5Hz, 2H), 4.9 (s, 6H), 5.3 (s, 1H), 7.3 (m, 1H), 7.5 (d, J=4.2Hz, 4H), 7.6 (m, 2H), 7.8 (m, 2H).

Example 42

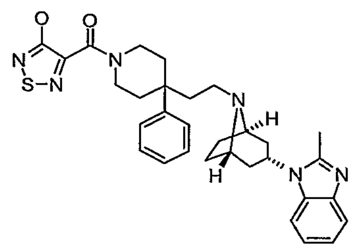
N-{4-[(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenyl-1-piperidinyl)carbonyl]-2-pyridinyl}acetamide



^{1}H NMR (400 MHz, methanol-d4) δ ppm 1.6 (m, 2H), 1.8 (m, 9H), 2.2 (m, 2H), 2.3 (m, 3H), 2.4 (m, 3H), 3.2 (m, 8H), 3.4 (m, 1H), 4.0 (m, 1H), 4.7 (m, 1H), 7.0 (dd, *J*=5.0, 1.4Hz, 1H), 7.1 (m, 2H), 7.2 (m, 1H), 7.3 (m, 5H), 7.4 (m, 1H), 8.0 (s, 1H), 8.3 (d, *J*=5.0Hz, 1H).

Example 39

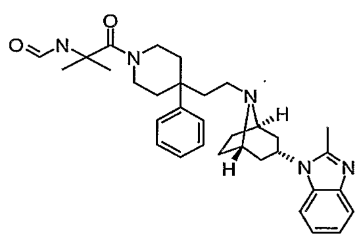
4-[(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenyl-1-piperidinyl)carbonyl]-1,2,5-thiadiazol-3-ol



^{1}H NMR (300 MHz, DMSO-d6) δ ppm 1.6 (d, *J*=7.5Hz, 2H), 1.8 (m, 7H), 2.1 (s, 2H), 2.3 (s, 2H), 2.5 (s, 3H), 2.5 (m, 2H), 3.1 (m, 1H), 3.4 (m, 6H), 3.8 (s, 1H), 4.5 (s, 1H), 7.1 (m, 2H), 7.2 (m, 1H), 7.4 (m, 5H), 7.5 (m, 1H).

Example 37

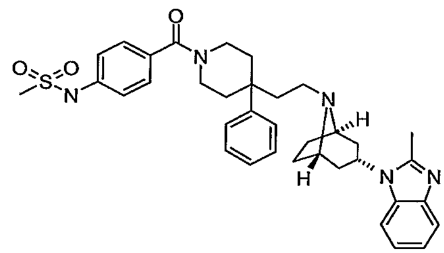
1,1-dimethyl-2-(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenyl-1-piperidinyl)-2-oxoethylformamide



^{1}H NMR (400 MHz, methanol-d4) δ ppm 1.5 (m, 6H), 1.7 (m, 2H), 1.9 (m, 8H), 2.2 (s, 2H), 2.4 (m, 2H), 2.5 (s, 3H), 3.3 (m, 4H), 3.3 (m, 2H), 3.6 (m, 1H), 4.0 (s, 2H, 4.7 (m, 1H), 7.2 (m, 2H), 7.2 (m, 1H), 7.4 (m, 5H), 7.5 (m, 1H), 8.0 (s, 1H).

Example 36

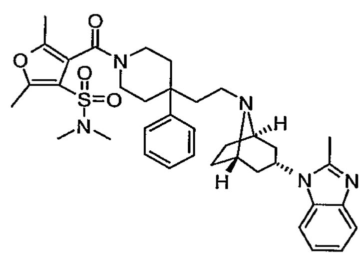
N-{4-[(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenyl-1-piperi-dinyl)carbonyl]phenyl}methanesulfonamide formate salt



[1]H NMR (400 MHz, methanol-d4) δ ppm 1.8 (m, 11H), 2.2 (m, 3H), 2.3 (m, 1H), 2.4 (m, 5H), 2.9 (m, 3H), 3.2 (m, 3H), 3.4 (m, 2H), 3.6 (m, 1H), 4.0 (m, *J*=4.3Hz, 1H), 4.7 (m, 1H), 7.1 (m, 2H), 7.2 (m, 1H), 7.2 (m, 2H), 7.3 (m, 6H), 7.4 (m, 1H).

Example 35

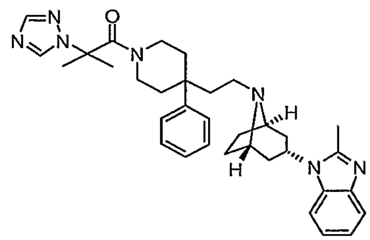
N,N,2,5-tetramethyl-4-[(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenyl-1-piperidinyl)carbonyl]-3-furansulfonamide formate salt



[1]H NMR (400 MHz, chloroform-d) δ ppm 1.6 (m, 2H), 1.8 (m, 8H), 2.1 (m, 5H), 2.3 (m, 4H), 2.4 (m, 6H), 2.6 (m, 3H), 2.7 (m, 3H), 3.1 (m, 2H), 3.3 (m, 2H), 3.4 (m, 1H), 4.0 (m, 1H), 4.7 (m, 1H), 7.1 (m, 2H), 7.1 (m, 1H), 7.3 (m, 5H), 7.4 (m, 1H).

Example 33

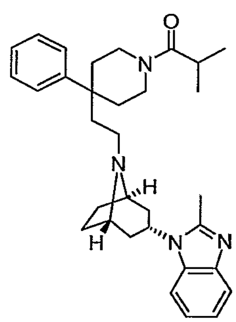
2-methyl-1-[(1R,5S)-8-(2-{1-[2-methyl-2-(1H-1,2,4-triazol-1-yl)propanoyl]-4-phenyl-4-piperidinyl}ethyl)-8-azabicyclo[3.2.1]oct-3-yl]-1H-benzimidazole



^{1}H NMR (300 MHz, chloroform-d) δ ppm 1.5 (m, 5H), 1.7 (d, *J*=15.1Hz, 3H), 1.9 (m, 10H), 2.0 (s, 2H), 2.4 (m, 3H), 2.6 (s, 3H), 3.0 (m, 5H), 4.6 (m, 1H), 7.2 (m, 5H), 7.3 (m, 3H), 7.6 (m, 1H), 8.0 (s, 1H), 8.1 (s, 1H).

Example 31

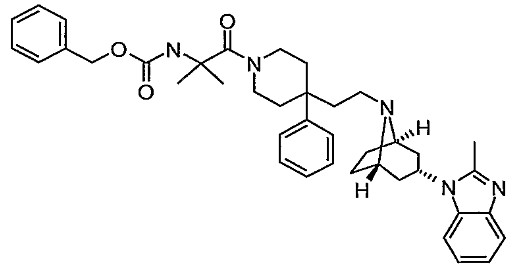
1-{(1R,5S)-8-[2-(1-isobutyryl-4-phenyl-4-piperidinyl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-2-methyl-1H-benzimidazole



^{1}H NMR (300 MHz, chloroform-d) δ ppm 1.1 (d, *J*=6.7Hz, 3H), 1.1 (d, *J*=6.7Hz, 3H), 1.2 (m, 2H), 1.6 (m, *J*=7.3, 7.3Hz, 2H), 1.8 (m, 8H), 2.2 (m, 2H) 2.4 (m, 2H), 2.5 (m, 3H), 2.8 (m, 1H), 3.2 (m, 4H), 3.7 (m, 1H), 4.0 (m, 1H), 4.7 (m, 1H), 7.2 (m, 3H), 7.3 (m, 5H), 7.7 (m, 1H).

Example 30

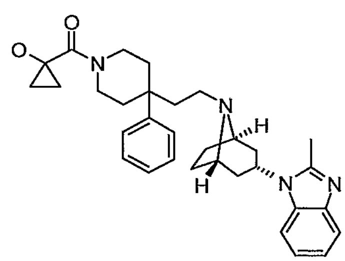
benzyl 1,1-dimethyl-2-(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenyl-1-piperidinyl)-2-oxoethylcarbamate



^{1}H NMR (400 MHz, chloroform-d) δ ppm 1.0 (m, *J*=7.1, 7.1Hz, 1H), 1.5 (m, 8H), 1.8 (d, *J*=6.1Hz, 4H), 1.9 (m, 7H), 2.1 (m, 3H), 2.3 (m, 2H), 2.5 (s, 3H), 3.3 (m, 4H), 4.6 (m, 1H), 5.0 (s, 2H), 7.1 (m, 3H), 7.3 (m, 8H), 7.4 (t, *J*=7.7Hz, 2H), 7.6 (m, 1H).

Example 29

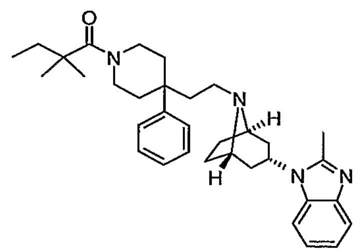
1-[(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenyl-1-piperidinyl)carbonyl]cyclopropanol



^{1}H NMR (400 MHz, chloroform-d) δ ppm 0.9 (m, *J*=20.3Hz, 2H), 1.0 (m, 2H), 1.3 (m, 4H), 1.6 (m, 3H), 1.8 (m, 6H), 2.2 (m, 2H), 2.4 (m, 2H), 2.6 (s, 3H), 3.2 (d, *J*=3.2Hz, 4H), 4.1 (m, 2H), 4.6 (m, 1H), 7.1 (m, 2H), 7.3 (m, 4H), 7.4 (t, *J*=7.7Hz, 2H), 7.6 (d, *J*=7.1Hz, 1H).

Example 28

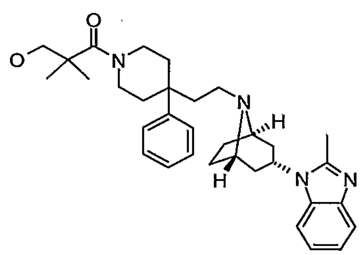
1-((1R,5S)-8-{2-[1-(2,2-dimethylbutanoyl)-4-phenyl-4-piperidinyl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1H-benzimidazole



^{1}H NMR (400 MHz, chloroform-d) δ ppm 0.9 (t, *J*=7.5Hz, 3H), 1.2 (s, 6H), 1.6 (m, 4H), 1.8 (m, 8H), 2.2 (dd, *J*=12.5, 3.2Hz, 2H), 2.3 (m, 2H), 2.5 (m, 1H), 2.6 (s, 3H), 3.0 (m, 1H), 3.2 (m, 4H), 3.9 (m, 2H), 4.6 (m, 1H), 7.1 (m, 2H), 7.2 (m, 1H), 7.3 (m, 3H), 7.4 (m, 2H), 7.6 (m, 1H).

Example 27

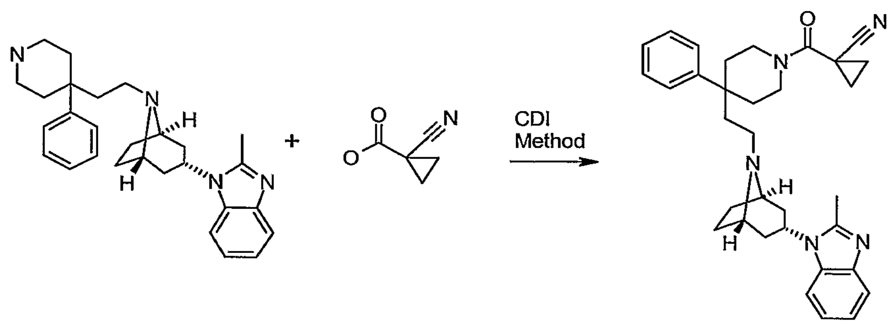
2,2-dimethyl-3-(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenyl-1-piperidinyl)-3-oxo-1-propanol



^{1}H NMR (400 MHz, chloroform-d) δ ppm 1.0 (d, *J*=6.8Hz, 2H), 1.2 (s, 6H), 1.6 (m, 2H), 1.8 (m, 4H), 1.9 (m, 4H), 2.2 (dd, *J*=12.0, 2.7Hz, 2H), 2.3 (m, 2H), 2.6 (s, 3H), 3.2 (m, *J*=11.1, 11.1Hz, 4H), 3.5 (s, 2H), 3.8 (m, 1H), 3.9 (d, *J*=13.2Hz, 2H), 4.6 (m, 1H), 7.1 (m, 2H), 7.3 (m, 4H), 7.4 (m, 2H), 7.6 (m, 1H).

Example 26

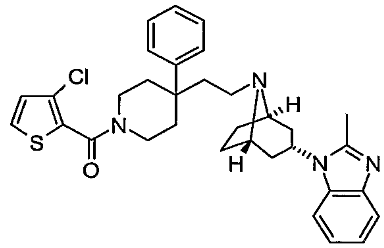
1-[(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenyl-1-piperidinyl)carbonyl]cyclopropanecarbonitrile



To a solution of 1-cyanocyclopropane-carboxylic acid (38.9 mg, 0.351 mmole) in 1 ml of DCE was added carbonyldiamidazole (38.0 mg, 0.234 mmole) and the mixture was stirred until gas evolution stopped. 2-Methyl-1-{(1*R*,5*S*)-8-[2-(4-phenyl-4-piperidinyl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1*H*-benzimidazole (50.0 mg, 0.117 mmole) was added and the resulting mixture was stirred overnight. The solvent was evaporated and the reaction mixture was flashed on silica using a gradient of 1-8% MeOH in $CHCl_3$ to afford 1-[(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenyl-1-piperidinyl)carbonyl]cyclopropanecarbonitrile. MS ES+ 522 (M+H). ^{1}H NMR (300 MHz, chloroform-d) δ ppm 1.6 (m, J=43.1Hz, 6H), 1.9 (d, J=25.3Hz, 10H), 2.4 (m, J=10.0Hz, 4H), 2.6 (s, 3H), 3.3 (m, 3H), 3.5 (m, 1H), 4.1 (m, 2H), 4.7 (m, 1H), 7.3 (m, 8H), 7.7 (m, 1H).

Example 25

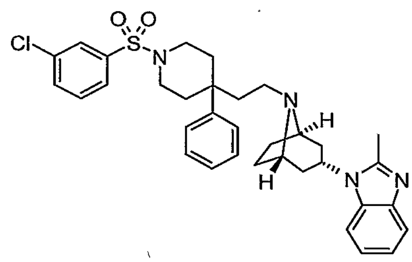
1-[(1R,5S)-8-(2-{1-[(3-chloro-2-thienyl)carbonyl]-4-phenyl-4-piperidinyl}ethyl)-8-azabicyclo[3.2.1]oct-3-yl]-2-methyl-1H-benzimidazole



^{1}H NMR (300 MHz, methanol-d4) δ ppm 0.9 (m, 1H), 1.1 (m, 3H), 1.6 (d, *J*=12.2Hz, 2H), 1.9 (m, 8H), 2.3 (m, 4H), 2.4 (s, 3H), 3.2 (m, 2H), 3.6 (m, 1H), 4.0 (m, *J*=7.1Hz, 1H), 4.7 (m, 1H), 6.9 (d, *J*=5.2Hz, 1H), 7.1 (m, 2H), 7.2 (d, *J*=6.2Hz, 1H), 7.3 (m, 5H), 7.4 (m, *J*=1.5Hz, 1H), 7.6 (d, *J*=5.2Hz, 1H).

Example 342

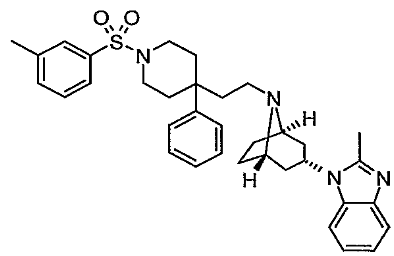
1-[(1R,5S)-8-(2-{1-[(3-chlorophenyl)sulfonyl]-4-phenyl-4-piperidinyl}ethyl)-8-azabicyclo[3.2.1]oct-3-yl]-2-methyl-1H-benzimidazole



^{1}H NMR (300 MHz, chloroform-d) δ ppm 1.6 (m, 2H), 1.7 (m, 4H), 1.9 (m, 8H), 2.4 (m, 4H), 2.6 (s, 3H), 2.8 (m, 2H), 3.4 (m, 2H), 4.6 (m, 1H), 7.2 (m, 5H), 7.3 (m, 3H), 7.4 (t, *J*=7.9Hz, 1H), 7.5 (m, 1H), 7.6 (d, *J*=7.8Hz, 1H), 7.7 (m, 1H), 7.7 (m, *J*=1.8, 1.8Hz, 1H).

Example 343

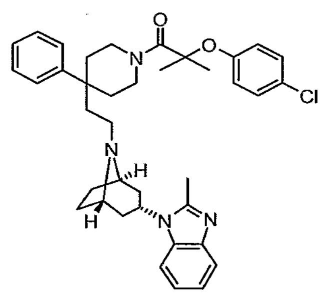
2-methyl-1-[(1R,5S)-8-(2-{1-[(3-methylphenyl)sulfonyl]-4-phenyl-4-piperidinyl}ethyl)-8-azabicyclo[3.2.1]oct-3-yl]-1H-benzimidazole



^{1}H NMR (300 MHz, chloroform-d) δ ppm 1.6 (m, 2H), 1.7 (dd, *J*=9.3, 5.6Hz, 2H), 1.9 (m, 8H), 2.3 (m, 4H), 2.4 (s, 3H), 2.5 (d, *J*=13.9Hz, 3H), 2.8 (m, 2H), 3.2 (m, 2H), 3.4 (m, 2H), 4.5 (m, 1H), 7.1 (m, 5H), 7.3 (m, 5H), 7.5 (m, 2H), 7.6 (m, 1H).

Example 344

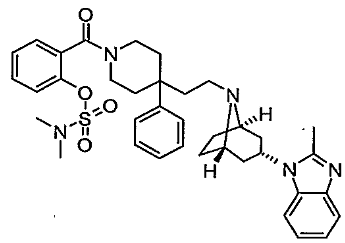
4-chlorophenyl 1,1-dimethyl-2-(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenyl-1-piperidinyl)-2-oxoethyl ether



^{1}H NMR (300 MHz, chloroform-d) δ ppm 1.3 (m, 1H), 1.6 (m, 11H), 1.9 (m, 7H), 2.2 (m, *J*=10.7Hz, 1H), 2.4 (m, *J*=23.3Hz, 2H), 2.6 (s, 3H), 3.1 (m, 1H), 3.2 (m, 2H), 3.4 (m, 1H), 4.2 (m, 2H), 4.6 (m, 1H), 6.8 (m, 2H), 7.2 (m, 8H), 7.3 (m, 2H), 7.7 (m, 1H).

Example 34

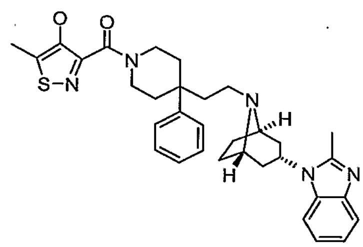
2-[(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenyl-1-piperi-dinyl)carbonyl]phenyl dimethylsulfamate formate salt



^{1}H NMR (400 MHz, chloroform-d) δ ppm 1.9 (m, 10H), 2.3 (m, 9H), 2.7 (s, 3H), 2.9 (s, 3H), 3.1 (m, 2H), 3.4 (m, 3H), 4.1 (m, *J*=13.6Hz, 1H), 4.7 (m, 1H), 7.1 (m, 2H), 7.2 (m, 4H), 7.3 (m, 4H), 7.4 (m, 2H), 7.4 (m, 1H).

Example 37

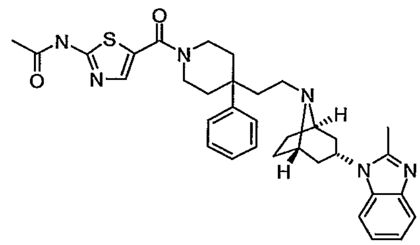
5-methyl-3-[(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenyl-1-piperidinyl)carbonyl]-4-isothiazolol



^{1}H NMR (300 MHz, DMSO-d6) δ ppm 2.7 (m, 3H), 3.1 (m, 4H), 3.3 (m, 10H), 3.6 (m, 2H), 3.8 (s, 6H), 4.0 (m, 3H), 4.2 (m, 1H), 4.7 (m, 1H), 8.6 (m, *J*=4.6, 4.6Hz, 2H), 8.7 (d, *J*=6.6Hz, 1H), 8.8 (d, *J*=14.8Hz, 5H), 8.9 (m, 1H).

Example 38

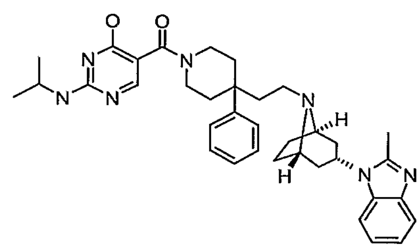
N-{5-[(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenyl-1-piperidinyl)carbonyl]-1,3-thiazol-2-yl}acetamide



^{1}H NMR (400 MHz, methanol-d4) δ ppm 1.6 (s, 1H), 2.0 (m, 12H), 2.5 (m, 5H), 3.1 (s, 2H), 3.2 (m, 2H), 3.5 (m, 4H), 3.7 (m, 2H), 4.0 (m, 2H), 7.1 (m, 4H), 7.3 (m, 5H), 7.5 (m, 1H).

Example 43

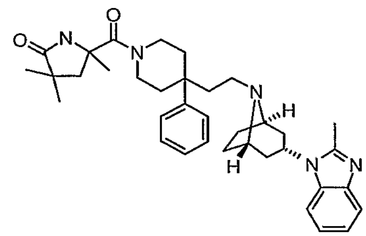
2-(isopropylamino)-5-[(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenyl-1-piperidinyl)carbonyl]-4-pyrimidinol



^{1}H NMR (400 MHz, DMSO-d6) δ ppm 1.1 (dd, *J*=20.0, 6.4Hz, 5H), 1.6 (d, *J*=7.8Hz, 2H), 1.8 (m, 8H), 2.1 (m, 2H), 2.4 (m, 2H), 2.5 (d, *J*=7.5Hz, 3H), 2.5 (m, 1H), 3.3 (m, 8H), 3.8 (m, *J*=21.0Hz, 1H), 4.0 (m, 1H), 4.5 (m, 1H), 6.7 (s, 1H), 7.1 (m, 2H), 7.2 (m, 1H), 7.4 (m, 5H), 7.5 (m, 1H), 7.8 (s, 1H).

Example 45

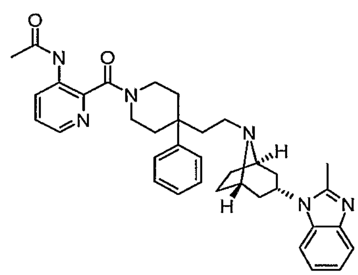
3,3,5-trimethyl-5-[(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenyl-1-piperidinyl)carbonyl]-2-pyrrolidinone



[1]H NMR (400 MHz, DMSO-d6) δ ppm 0.9 (m, 3H), 1.1 (s, 3H), 1.4 (m, 2H), 1.6 (m, 2H), 1.8 (m, 8H), 2.0 (m, 3H), 2.3 (m, 3H), 2.5 (m, 1H), 3.3 (m, 4H), 3.3 (d, *J*=11.1Hz, 5H), 3.7 (m, *J*=1.4Hz, 2H), 4.5 (m, 1H), 7.1 (m, 2H), 7.2 (m, 1H), 7.4 (m, 5H), 7.5 (m, 1H), 7.8 (s, 1H).

Example 46

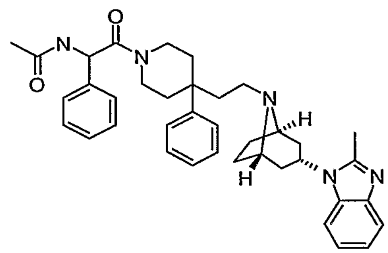
N-{2-[(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenyl-1-piperidinyl)carbonyl]-3-pyridinyl}acetamide



[1]H NMR (400 MHz, DMSO-d6) δ ppm 1.6 (m, 2H), 1.8 (m, 8H), 2.0 (s, 3H), 2.2 (m, 2H), 2.4 (m, 2H), 2.4 (s, 3H), 2.5 (m, 2H), 3.1 (m, 1H), 3.3 (m, 3H), 3.4 (dd, *J*=7.0, 3.0Hz, 1H), 3.9 (m, 1H), 4.5 (m, 1H), 7.1 (m, 2H), 7.2 (m, 1H), 7.4 (m, 5H), 7.4 (dd, *J*=8.2, 4.6Hz, 1H), 7.5 (m, 1H), 8.0 (m, 1H), 8.3 (m, 1H), 9.7 (s, 1H).

Example 52

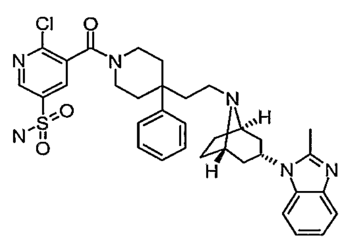
N-[2-(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenyl-1-piperidinyl)-2-oxo-1-phenylethyl]acetamide



[1]H NMR (400 MHz, DMSO-d6) δ ppm 1.6 (m, 3H), 1.8 (m, 9H), 2.0 (m, 2H), 2.4 (m, 2H), 2.5 (m, 3H), 3.2 (m, 4H), 3.4 (d, *J*=11.4Hz, 3H), 3.6 (m, 2H), 3.8 (m, 1H), 4.5 (m, 1H), 5.9 (dd, *J*=24.6, 7.8Hz, 1H), 7.1 (m, 2H), 7.3 (m, 10H), 7.5 (d, *J*=7.1Hz, 1H), 8.5 (dd, *J*=7.8, 5.4Hz, 1H).

Example 59

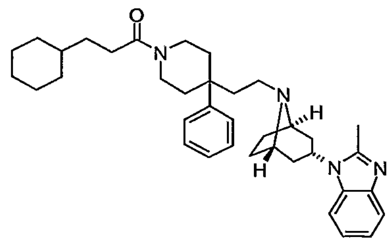
6-chloro-5-[(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenyl-1-piperidinyl)carbonyl]-3-pyridinesulfonamide



[1]H NMR (400 MHz, methanol-d4) δ ppm 1.6 (m, 2H), 1.8 (m, 8H), 2.0 (d, *J*=6.6Hz, 2H), 2.2 (d, *J*=7.7Hz, 2H), 2.4 (m, 4H), 2.5 (s, 3H), 3.1 (m, 2H), 3.3 (m, 3H), 4.1 (m, 1H), 4.7 (s, 1H), 7.1 (m, 2H), 7.2 (m, 1H), 7.3 (m, 5H), 7.4 (m, 1H), 8.2 (m, *J*=61.5, 2.4Hz, 1H), 8.8 (dd, *J*=2.4, 1.5Hz, 1H).

Example 345

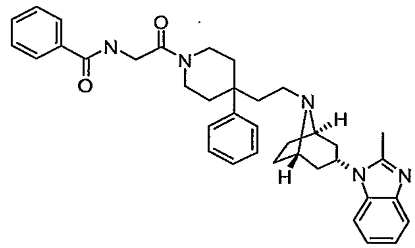
1-((1R,5S)-8-{2-[1-(3-cyclohexylpropanoyl)-4-phenyl-4-piperidinyl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1H-benzimidazole



^{1}H NMR (400 MHz, methanol-d4) δ ppm 0.8 (m, 2H), 1.2 (m, 4H), 1.4 (q, *J*=7.4Hz, 2H), 1.8 (m, 16H), 2.2 (m, 2H), 2.3 (m, 4H), 2.5 (s, 3H), 3.1 (m, 1H), 3.2 (m, 4H), 3.7 (dd, *J*=9.5, 4.8Hz, 1H), 3.9 (m, 1H), 4.7 (m, 1H), 7.1 (m, 3H), 7.3 (m, 5H), 7.4 (m, 1H).

Example 346

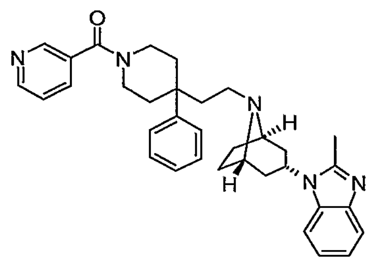
N-[2-(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenyl-1-piperidinyl)-2-oxoethyl]benzamide



^{1}H NMR (400 MHz, methanol-d4) δ ppm 1.7 (m, 2H), 1.9 (m, 10H), 2.4 (m, 4H), 2.5 (m, *J*=3.6Hz, 3H), 3.2 (m, 1H), 3.3 (m, 4H), 3.8 (m, 1H), 4.0 (m, 1H), 4.3 (m, 2H), 4.7 (m, 1H), 7.2 (m, 3H), 7.4 (m, 7H), 7.5 (m, 2H), 7.9 (m, 1H).

Example 347

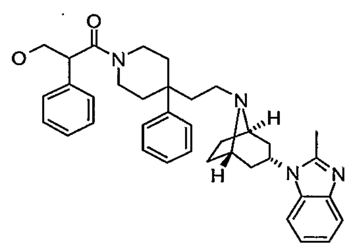
2-methyl-1-((1R,5S)-8-{2-[4-phenyl-1-(3-pyridinyl carbonyl)-4-piperidinyl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-1H-benzimidazole



^{1}H NMR (400 MHz, methanol-d4) δ ppm 1.6 (m, 2H), 1.9 (m, 10H), 2.2 (m, 1H), 2.3 (m, 4H), 2.4 (s, 3H), 3.2 (m, 3H), 3.5 (m, 1H), 4.1 (m, *J*=13.2Hz, 1H), 4.7 (m, 1H), 7.1 (m, 3H), 7.3 (m, 5H), 7.4 (m, 2H), 7.8 (m, 1H), 8.5 (d, *J*=1.4Hz, 1H), 8.6 (dd, *J*=5.0, 1.8Hz, 1H).

Example 348

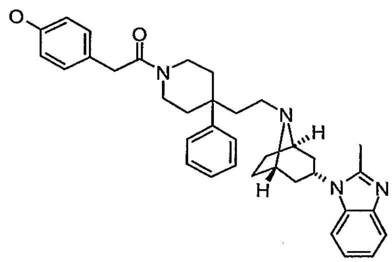
3-(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenyl-1-piperidinyl)-3-oxo-2-phenyl-1-propanol



^{1}H NMR (400 MHz, methanol-d4) δ ppm 1.6 (m, 2H), 1.8 (m, 10H), 2.1 (m, 1H), 2.4 (m, 2H), 2.5 (s, 3H), 2.5 (s, 2H), 3.1 (m, 3H), 3.3 (m, 2H), 3.7 (m, 2H), 4.1 (m, 2H), 4.7 (m, 1H), 7.3 (m, 13H), 7.5 (m, 1H).

Example 349

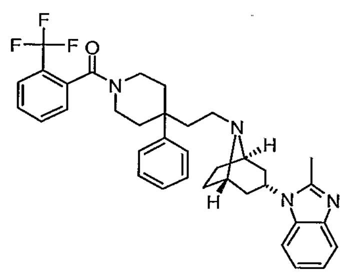
4-[2-(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenyl-1-piperidinyl)-2-oxoethyl]phenol



^{1}H NMR (400 MHz, methanol-d4) δ ppm 1.4 (m, 1H), 1.6 (m, 1H), 2.0 (m, 8H), 2.3 (m, 2H), 2.4 (s, 3H), 2.5 (m, 2H), 3.0 (m, 1H), 3.1 (m, 1H), 3.4 (s, 1H), 3.6 (m, 5H), 3.9 (m, 1H), 4.9 (m, 1H), 6.6 (m, 2H), 7.0 (m, 2H), 7.2 (m, 3H), 7.3 (m, 5H), 7.4 (m, 1H), 7.5 (m, 1H).

Example 350

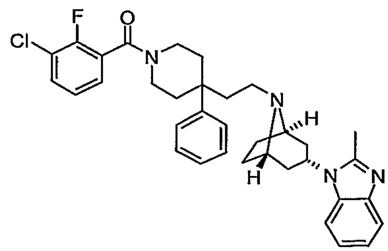
2-methyl-1-[(1R,5S)-8-(2-{4-phenyl-1-[2-(trifluoromethyl)benzoyl]-4-piperidinyl}ethyl)-8-azabicyclo[3.2.1]oct-3-yl]-1H-benzimidazole



^{1}H NMR (400 MHz, methanol-d4) δ ppm 1.8 (m, 10H), 2.1 (m, 3H), 2.4 (m, 6H), 3.0 (m, 2H), 3.2 (m, 1H), 3.4 (m, 2H), 4.1 (m, 1H), 4.7 (m, 1H), 7.1 (m, 3H), 7.3 (m, 1H), 7.3 (m, 5H), 7.4 (m, 1H), 7.6 (m, 3H).

Example 351

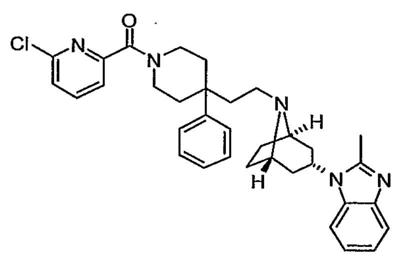
1-((1R,5S)-8-{2-[1-(3-chloro-2-fluorobenzoyl)-4-phenyl-4-piperidinyl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1H-benzimidazole



^1H NMR (400 MHz, methanol-d4) δ ppm 1.7 (m, 2H), 1.9 (m, 10H), 2.3 (m, 1H), 2.4 (m, 3H), 2.5 (s, 3H), 3.2 (m, 2H), 3.4 (m, 1H), 3.4 (m, 2H), 4.2 (m, 1H), 4.7 (m, 1H), 7.2 (m, 2H), 7.3 (m, 2H), 7.4 (m, 6H), 7.5 (m, 1H), 7.6 (m, 1H).

Example 352

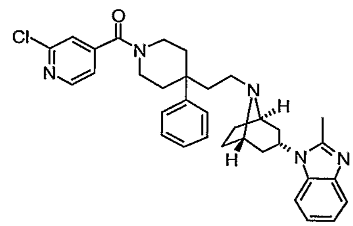
1-[(1R,5S)-8-(2-{1-[(6-chloro-2-pyridinyl)carbonyl]-4-phenyl-4-piperidinyl}ethyl)-8-azabicyclo[3.2.1]oct-3-yl]-2-methyl-1H-benzimidazole



^1H NMR (400 MHz, methanol-d4) δ ppm 1.6 (m, 2H), 1.9 (m, 10H), 2.2 (m, 1H), 2.4 (m, 3H), 2.4 (s, 3H), 3.2 (m, 1H), 3.3 (m, 3H), 3.5 (m, 1H), 4.1 (m, 1H), 4.7 (m, 1H), 7.1 (m, 3H), 7.3 (m, 5H), 7.4 (m, 3H), 7.8 (t, *J*=7.7Hz, 1H).

Example 353

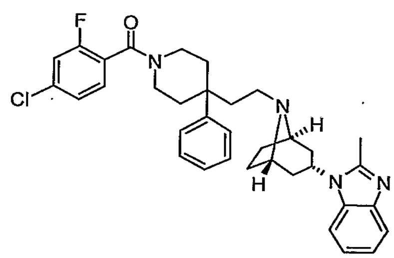
1-((1R,5S)-8-{2-[1-(2-chloroisonicotinoyl)-4-phenyl-4-piperidinyl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1H-benzimidazole



^{1}H NMR (400 MHz, methanol-d4) δ ppm 1.7 (m, 2H), 1.9 (m, 10H), 2.3 (m, 1H), 2.4 (m, 3H), 2.5 (s, 3H), 2.6 (m, 1H), 3.3 (m, 3H), 3.5 (m, 1H), 4.2 (m, 1H), 4.7 (m, 1H), 7.2 (m, 3H), 7.4 (m, 6H), 7.5 (m, 2H), 8.5 (d, *J*=5.0Hz, 1H).

Example 354

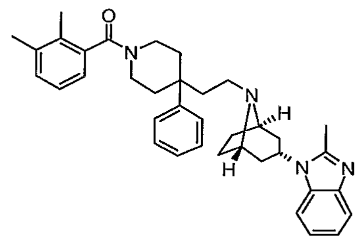
1-((1R,5S)-8-{2-[1-(4-chloro-2-fluorobenzoyl)-4-phenyl-4-piperidinyl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1H-benzimidazole



^{1}H NMR (400 MHz, methanol-d4) δ ppm 1.6 (m, 2H), 1.8 (m, 10H), 2.2 (m, 1H), 2.3 (m, 3H), 2.4 (s, 3H), 2.5 (m, 1H), 3.1 (m, 1H), 3.3 (m, 2H), 3.4 (m, 1H), 4.1 (m, 1H), 4.6 (m, 1H), 7.1 (m, 2H), 7.2 (m, 1H), 7.3 (m, 8H), 7.4 (m, 1H).

Example 355

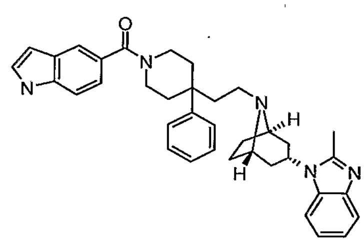
1-((1R,5S)-8-{2-[1-(2,3-dimethylbenzoyl)-4-phenyl-4-piperidinyl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1H-benzimidazole



^{1}H NMR (400 MHz, methanol-d4) δ ppm 1.8 (m, 10H), 2.0 (s, 3H), 2.1 (m, 1H), 2.2 (m, 3H), 2.3 (m, 4H), 2.4 (m, 3H), 2.5 (m, 1H), 3.0 (m, 1H), 3.3 (m, 4H), 4.1 (m, 1H), 4.6 (m, 1H), 6.8 (d, *J*=7.1Hz, 1H), 7.1 (m, 5H), 7.3 (m, 5H), 7.4 (m, 1H).

Example 356

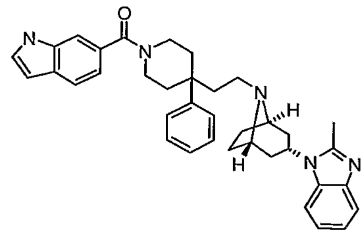
1-((1R,5S)-8-{2-[1-(1H-indol-5-ylcarbonyl)-4-phenyl-4-piperidinyl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1H-benzimidazole



^{1}H NMR (400 MHz, methanol-d4) δ ppm 1.6 (m, 2H), 1.9 (m, 10H), 2.2 (m, 3H), 2.4 (m, 4H), 3.3 (m, 2H), 3.7 (m, 1H), 4.1 (m, 1H), 4.5 (m, 2H), 4.7 (m, 1H), 6.4 (d, *J*=2.5Hz, 1H), 7.1 (m, 2H), 7.2 (m, 1H), 7.2 (d, *J*=3.2Hz, 1H), 7.3 (m, 8H), 7.4 (m, 1H), 7.6 (s, 1H).

Example 357

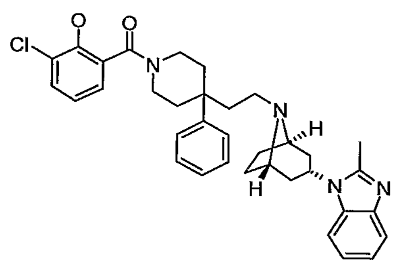
1-((1R,5S)-8-{2-[1-(1H-indol-6-ylcarbonyl)-4-phenyl-4-piperidinyl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1H-benzimidazole



^{1}H NMR (400 MHz, methanol-d4) δ ppm 1.2 (m, 2H), 1.6 (m, 2H), 1.8 (m, 8H), 2.2 (m, 5H), 2.4 (m, 3H), 2.5 (m, 1H), 3.3 (m, 2H), 3.6 (m, 1H), 4.0 (m, 1H), 4.6 (m, 1H), 6.4 (d, *J*=2.1Hz, 1H), 7.0 (dd, *J*=7.8, 1.4Hz, 1H), 7.1 (m, 2H), 7.2 (m, 1H), 7.3 (d, *J*=3.2Hz, 1H), 7.3 (m, 6H), 7.4 (s, 1H), 7.4 (m, 1H), 7.5 (m, 1H).

Example 358

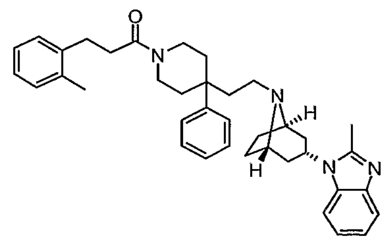
2-chloro-6-[(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenyl-1-piperidinyl)carbonyl]phenol



^{1}H NMR (400 MHz, methanol-d4) δ ppm 1.3 (m, 2H), 1.7 (m, 2H), 2.0 (m, 10H), 2.4 (m, 5H), 2.5 (m, 3H), 3.6 (m, 2H), 4.1 (m, 1H), 4.7 (m, 1H), 6.9 (t, *J*=7.7Hz, 1H), 7.1 (d, *J*=7.5Hz, 1H), 7.2 (m, 3H), 7.4 (m, 6H), 7.5 (m, 1H).

Example 359

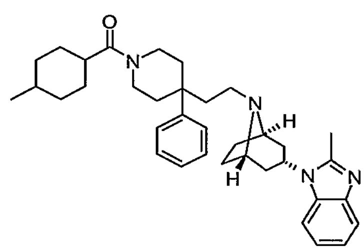
2-methyl-1-[(1R,5S)-8-(2-{1-[3-(2-methylphenyl) propanoyl]-4-phenyl-4-piperidinyl}ethyl)-8-azabicyclo[3.2.1]oct-3-yl]-1H-benzimidazole



^{1}H NMR (400 MHz, methanol-d4) δ ppm 1.2 (m, 1H), 1.4 (m, 1H), 1.6 (m, 4H), 1.9 (m, 6H), 2.1 (m, 1H), 2.3 (m, 3H), 2.3 (m, 2H), 2.5 (m, 3H), 2.6 (m, 4H), 2.8 (m, 2 H), 3.0 (m, 2H), 3.2 (d, *J*=5.7 Hz, 1H), 3.5 (m, 1H), 3.9 (m, 1H), 4.6 (m, 1H), 7.0 (m, 2H), 7.0 (m, 2H), 7.1 (m, 2H), 7.1 (m, 1H), 7.3 (m, 5H), 7.4 (m, 1H).

Example 360

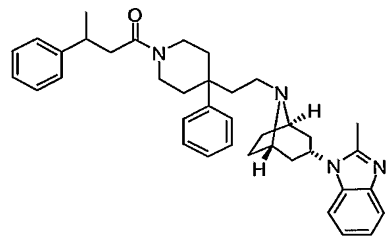
2-methyl-1-[(1R,5S)-8-(2-{1-[(4-methylcyclohexyl) carbonyl]-4-phenyl-4-piperidinyl}ethyl)-8-azabicyclo[3.2.1]oct-3-yl]-1H-benzimidazole



^{1}H NMR (400 MHz, methanol-d4) δ ppm 0.8 (m, 2H), 0.9 (m, 4H), 1.5 (m, 18H), 2.3 (m, 4H), 2.5 (m, 3H), 2.5 (m, 1H), 3.1 (m, 1H), 3.2 (m, 3H), 3.7 (m, 1H), 3.9 (m, 1H), 4.7 (m, 1H), 7.1 (m, 2H), 7.2 (m, 1H), 7.3 (m, 5H), 7.4 (m, 1H).

Example 361

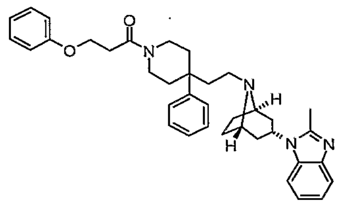
2-methyl-1-((1R,5S)-8-{2-[4-phenyl-1-(3-phenyl-butanoyl)-4-piperidinyl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-1H-benzimidazole



^{1}H NMR (400 MHz, methanol-d4) δ ppm 1.2 (m, 4H), 1.4 (m, 1H), 1.6 (m, 3H), 1.9 (m, 8H), 2.3 (m, 2H), 2.5 (m, 1H), 2.7 (m, 2H), 3.0 (m, 2H), 3.0 (m, 1H), 3.2 (m, 4H), 3.5 (m, 1H), 3.7 (m, 1H), 3.9 (m, 1H), 4.7 (m, 1H), 7.1 (m, 5H), 7.3 (m, 8H), 7.4 (m, 1H).

Example 362

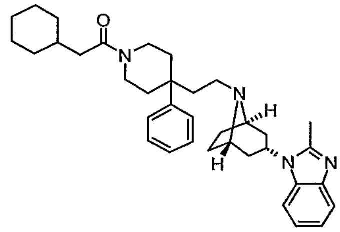
3-(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenyl-1-piperidinyl)-3-oxopropyl phenyl ether



^{1}H NMR (400 MHz, methanol-d4) δ ppm 1.3 (m, 4H), 1.8 (m, 10H), 2.4 (m, 4H), 2.5 (s, 3H), 2.6 (m, 1H), 2.9 (m, 2H), 3.2 (m, 1H), 3.4 (m, 2H), 3.8 (m, 1H), 4.0 (m, 1H), 4.8 (m, 1H), 6.9 (m, 3H), 7.2 (m, 5H), 7.4 (m, 5H), 7.5 (m, 1H).

Example 363

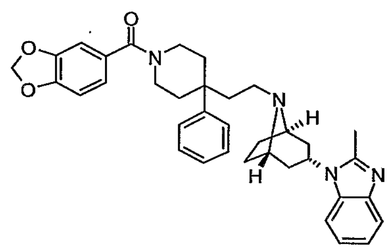
1-((1R,5S)-8-{2-[1-(cyclohexylacetyl)-4-phenyl-4-piperidinyl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1H-benzimidazole



^{1}H NMR (400 MHz, methanol-d4) δ ppm 1.0 (m, 2H), 1.2 (m, 3H), 1.7 (m, 9H), 1.9 (m, 11H), 2.3 (m, 4H), 2.4 (m, 2H), 2.5 (s, 3H), 3.2 (m, 1H), 3.3 (m, 1H), 3.8 (m, 1H), 4.0 (m, 1H), 4.8 (m, 1H), 7.2 (m, 2H), 7.2 (m, 1H), 7.4 (m, 5H), 7.5 (m, 1H).

Example 62

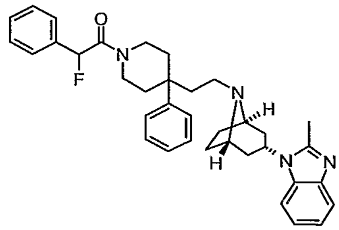
1-((1R,5S)-8-{2-[1-(1,3-benzodioxol-5-ylcarbonyl)-4-phenyl-4-piperidinyl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1H-benzimidazole



^{1}H NMR (400 MHz, methanol-d4) δ ppm 1.3 (m, 2H), 1.7 (m, 2H), 1.9 (m, 11H), 2.3 (m, 5H), 2.5 (d, *J*=6.4Hz, 3H), 2.6 (m, 1H), 3.3 (m, 1H), 3.7 (m, 1H), 4.1 (m, 1H), 4.7 (m, 1H), 6.9 (m, 2H), 7.2 (m, 2H), 7.2 (m, 1H), 7.4 (m, 6H), 7.5 (m, 1H).

Example 63

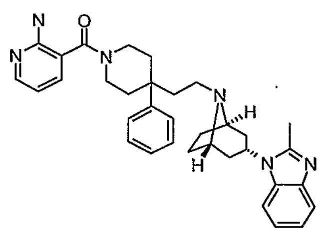
1-[(1R,5S)-8-(2-{1-[fluoro(phenyl)acetyl]-4-phenyl-4-piperidinyl}ethyl)-8-azabicyclo[3.2.1]oct-3-yl]-2-methyl-1H-benzimidazole



^{1}H NMR (400 MHz, methanol-d4) δ ppm 1.9 (m, 14H), 2.3 (m, 3H), 2.5 (m, 3H), 3.0 (m, 3H), 3.6 (m, 1H), 4.0 (m, 1H), 4.7 (m, 1H), 6.3 (dd, *J*=48.3, 20.9Hz, 1H), 7.3 (m, 14H).

Example 64

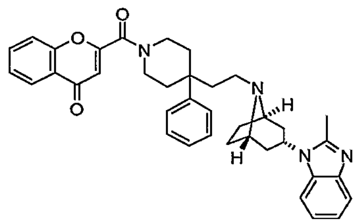
3-[(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenyl-1-piperidinyl)carbonyl]-2-pyridinylamine



^{1}H NMR (400 MHz, methanol-d4) δ ppm 1.7 (m, 2H), 1.9 (m, 10H), 2.3 (m, 4H), 2.5 (s, 3H), 3.3 (m, 2H), 3.8 (m, 4H), 4.7 (m, 1H), 6.7 (dd, *J*=7.3, 5.2Hz, 1H), 7.2 (m, 3H), 7.4 (m, 5H), 7.5 (m, 1H), 8.0 (dd, *J*=5.2, 2.0Hz, 1H).

Example 66

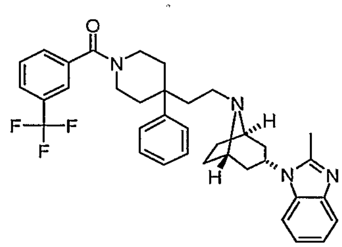
2-[(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenyl-1-piperidinyl)carbonyl]-4H-chromen-4-one



^{1}H NMR (400 MHz, methanol-d4) δ ppm 1.3 (m, 3H), 1.7 (m, 2H), 2.0 (m, 8H), 2.4 (m, 4H), 2.5 (m, 3H), 2.9 (m, 1H), 3.1 (m, 1H), 3.3 (m, 2H), 3.6 (m, 1H), 4.1 (m, 1H), 4.8 (m, 1H), 7.2 (m, 2H), 7.3 (m, 1H), 7.4 (m, 5H), 7.5 (m, 2H), 7.6 (d, *J*=7.8Hz, 1H), 7.8 (m, 1H), 8.2 (dd, *J*=8.0, 1.6Hz, 1H).

Example 67

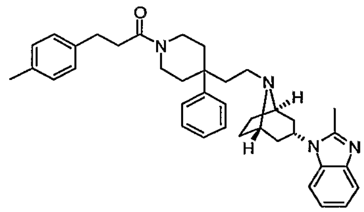
2-methyl-1-[(1R,5S)-8-(2-{4-phenyl-1-[3-(trifluoromethyl)benzoyl]-4-piperidinyl}ethyl)-8-azabicyclo[3.2.1]oct-3-yl]-1H-benzimidazole



^{1}H NMR (400 MHz, methanol-d4) δ ppm 1.3 (m, 1H), 1.7 (m, 2H), 1.9 (m, 10H), 2.3 (m, 1H), 2.4 (m, 4H), 2.5 (s, 3H), 3.3 (m, 2H), 3.5 (m, 1H), 4.2 (m, 1H), 4.7 (m, 1H), 7.2 (m, 2H), 7.2 (m, 1H), 7.4 (m, 5H), 7.5 (m, 1H), 7.7 (m, 2H), 7.7 (s, 1H), 7.8 (m, 1H).

Example 71

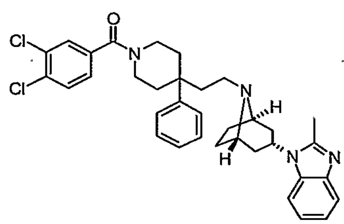
2-methyl-1-[(1R,5S)-8-(2-{1-[3-(4-methylphenyl) propanoyl]-4-phenyl-4-piperidinyl}ethyl)-8-azabicyclo[3.2.1]oct-3-yl]-1H-benzimidazole



^{1}H NMR (400 MHz, methanol-d4) δ ppm 1.5 (m, 1H), 1.7 (m, 4H), 1.8 (m, 2H), 1.9 (m, 10H), 2.2 (m, 1H), 2.2 (s, 3H), 2.4 (m, 2H), 2.5 (m, 3H), 2.8 (m, 2H), 3.2 (m, 2H), 3.6 (m, 1H), 3.9 (m, 1H), 4.7 (m, 1H), 7.1 (m, 3H), 7.2 (m, 3H), 7.4 (m, 6H), 7.5 (m, 1H).

Example 72

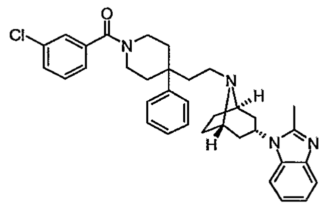
1-((1R,5S)-8-{2-[1-(3,4-dichlorobenzoyl)-4-phenyl-4-piperidinyl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1H-benzimidazole



^{1}H NMR (400 MHz, methanol-d4) δ ppm 1.7 (m, 2H), 1.9 (m, 11H), 2.3 (m, 1H), 2.4 (m, 4H), 2.5 (m, 3H), 3.3 (m, 2H), 3.6 (m, 1H), 4.1 (m, 1H), 4.7 (m, 1H), 7.2 (m, 2H), 7.2 (m, 1H), 7.3 (dd, *J*=8.2, 1.8Hz, 1H), 7.4 (m, 5H), 7.5 (m, 1H), 7.6 (m, 2H).

Example 73

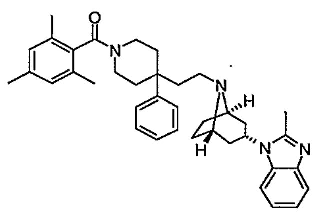
1-((1R,5S)-8-{2-[1-(3-chlorobenzoyl)-4-phenyl-4-piperidinyl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1H-benzimidazole



^{1}H NMR (400 MHz, methanol-d4) δ ppm 1.7 (m, 2H), 1.9 (m, 10H), 2.2 (m, 1H), 2.4 (m, 3H), 2.5 (s, 3H), 3.3 (m, 4H), 3.6 (m, 1H), 4.1 (m, *J*=11.1, 4.3Hz, 1H), 4.7 (m, 1H), 7.2 (m, 2H), 7.2 (m, 1H), 7.3 (m, 1H), 7.4 (m, 5H), 7.4 (m, 2H), 7.5 (m, 1H).

Example 74

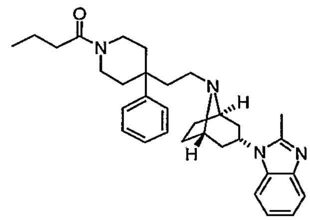
1-((1R,5S)-8-{2-[1-(mesitylcarbonyl)-4-phenyl-4-piperidinyl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1H-benzimidazole



^{1}H NMR (400 MHz, methanol-d4) δ ppm 1.7 (m, 2H), 1.8 (m, 1H), 1.9 (m, 10H), 2.1 (s, 3H), 2.2 (m, 1H), 2.3 (m, 6H), 2.4 (m, 3H), 2.5 (m, 3H), 3.1 (m, 1H), 3.3 (m, 3H), 4.2 (m, 1H), 4.7 (m, 1H), 6.9 (s, 1H), 7.2 (m, 2H), 7.2 (m, 1H), 7.4 (m, 5H), 7.5 (m, 1H).

Example 78

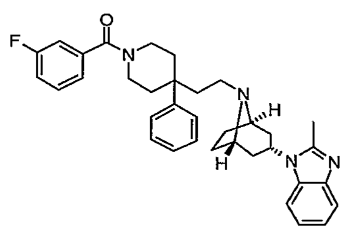
1-{(1R,5S)-8-[2-(1-butyryl-4-phenyl-4-piperidinyl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-2-methyl-1H-benzimidazole



^{1}H NMR (400 MHz, methanol-d4) δ ppm 1.0 (t, *J*=7.4Hz, 3H), 1.6 (m, 4H), 1.9 (m, 10H), 2.4 (m, 7H), 2.5 (s, 3H), 3.2 (m, 1H), 3.3 (m, 2H), 3.7 (m, 1H), 4.0 (d, *J*=3.7 Hz, 1H), 4.7 (m, 1H), 7.2 (m, 2H), 7.2 (m, 1H), 7.4 (m, 5H), 7.5 (m, 1H).

Example 79

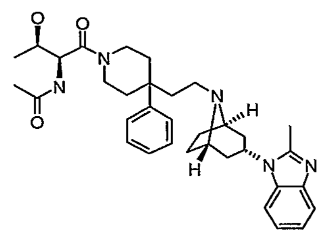
1-((1R,5S)-8-{2-[1-(3-fluorobenzoyl)-4-phenyl-4-piperidinyl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1H-benzimidazole



^{1}H NMR (400 MHz, methanol-d4) δ ppm 1.7 (m, 2H), 2.0 (m, 10H), 2.2 (m, 1H), 2.4 (m, 3H), 2.5 (m, 3H), 3.3 (m, 4H), 3.5 (m, *J*=5.6, 1.6Hz, 1H), 4.1 (m, *J*=4.0Hz, 1H), 4.7 (m, 1H), 7.2 (m, 6H), 7.4 (m, 5H), 7.5 (m, 1H), 7.5 (m, 1H).

Example 81

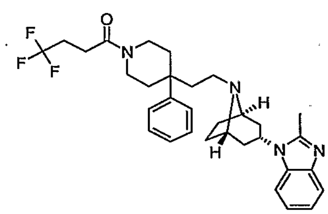
N-{(1S,2R)-2-hydroxy-1-[(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenyl-1-piperidinyl)carbonyl]propyl}acetamide



^{1}H NMR (400 MHz, methanol-d4) δ ppm 1.2 (m, 3H), 1.7 (m, 2H), 1.9 (m, 13H), 2.4 (m, 5H), 2.5 (s, 3H), 3.3 (m, 5H), 4.0 (m, 3H), 4.8 (m, 2H), 7.2 (m, 2H), 7.2 (m, 1H), 7.4 (m, 5H), 7.5 (m, 1H).

Example 82

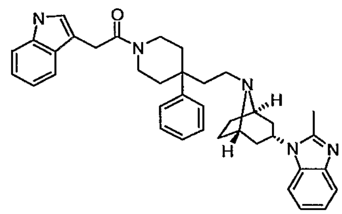
2-methyl-1-((1R,5S)-8-{2-[4-phenyl-1-(4,4,4-trifluorobutanoyl)-4-piperidinyl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-1H-benzimidazole



^{1}H NMR (400 MHz, methanol-d4) δ ppm 1.7 (m, 2H), 1.9 (m, 10H), 2.3 (m, 2H), 2.5 (m, 4H), 2.5 (s, 3H), 2.7 (m, 2H), 3.2 (m, 1H), 3.3 (m, 3H), 3.7 (m, 1H), 4.0 (m, 1H), 4.7 (m, 1H), 7.2 (m, 2H), 7.2 (m, 1H), 7.4 (m, 5H), 7.5 (m, 1H).

Example 83

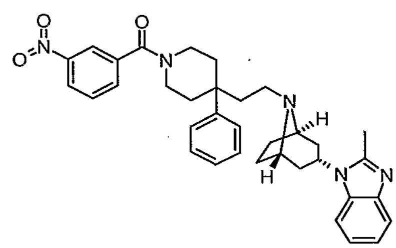
1-((1R,5S)-8-{2-[1-(1H-indol-3-ylacetyl)-4-phenyl-4-piperidinyl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1H-benzimidazole



^{1}H NMR (400 MHz, methanol-d4) δ ppm 1.4 (m, 1H), 1.7 (m, 6H), 1.9 (m, 6H), 2.0 (m, 1H), 2.2 (m, 1H), 2.4 (m, 2H), 2.5 (s, 3H), 3.1 (m, 1H), 3.2 (m, 3H), 3.8 (m, 2H), 3.9 (m, 1H), 4.1 (m, 1H), 4.7 (m, 1H), 7.0 (t, *J*=7.0Hz, 1H), 7.1 (m, 2H), 7.2 (m, 3H), 7.4 (m, 6H), 7.5 (m, 1H), 7.6 (d, *J*=7.8Hz, 1H).

Example 85

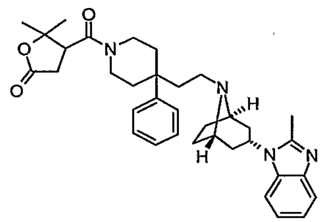
2-methyl-1-((1R,5S)-8-{2-[1-(3-nitrobenzoyl)-4-phenyl-4-piperidinyl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-1H-benzimidazole



^{1}H NMR (400 MHz, methanol-d4) δ ppm 1.7 (m, 2H), 2.0 (m, 12H), 2.3 (m, 1H), 2.4 (m, 3H), 2.5 (s, 3H), 3.3 (m, 2H), 3.6 (m, 1H), 4.2 (m, *J*=13.6Hz, 1H), 4.7 (m, 1H), 7.2 (m, 3H), 7.4 (m, 5H), 7.5 (m, 1H), 7.7 (t, *J*=7.8Hz, 1H), 7.8 (d, *J*=7.8Hz, 1H), 8.3 (s, 1H), 8.3 (d, *J*=8.2 Hz, 1H).

Example 86

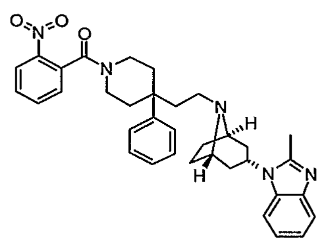
5,5-dimethyl-4-[(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenyl-1-piperidinyl)carbonyl]dihydro-2(3H)-furanone



^{1}H NMR (400 MHz, methanol-d4) δ ppm 1.2 (m, 2H), 1.5 (m, 3H), 1.9 (m, 14H), 2.4 (m, 4H), 2.5 (s, 3H), 2.8 (m, 2H), 3.1 (m, 1H), 3.4 (m, 2H), 3.8 (m, 2H), 4.1 (m, 1H), 4.8 (m, 1H), 7.2 (m, 3H), 7.4 (m, 5H), 7.5 (m, 1H).

Example 88

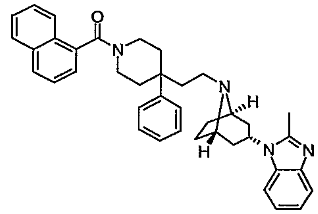
2-methyl-1-((1R,5S)-8-{2-[1-(2-nitrobenzoyl)-4-phenyl-4-piperidinyl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-1H-benzimidazole



^{1}H NMR (400 MHz, methanol-d4) δ ppm 1.3 (m, 1H), 1.7 (m, 2H), 2.0 (m, 10H), 2.2 (m, 1H), 2.4 (m, 3H), 2.5 (m, *J*=1.4 Hz, 3H), 3.2 (m, 2H), 3.4 (m, 2H), 4.2 (m, 1H), 4.7 (m, 1H), 7.2 (m, 2H), 7.3 (m, 1H), 7.4 (m, 6H), 7.5 (m, 1H), 7.7 (m, 1H), 7.8 (m, 1H), 8.2 (m, 1H).

Example 90

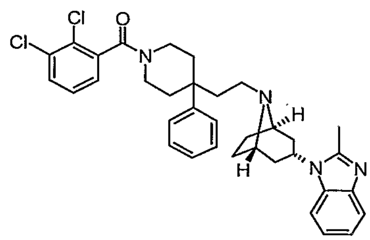
2-methyl-1-((1R,5S)-8-{2-[1-(1-naphthoyl)-4-phenyl-4-piperidinyl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-1H-benzimidazole



^{1}H NMR (400 MHz, methanol-d4) δ ppm 0.6 (m, 2H), 1.8 (m, 12H), 2.4 (m, 4H), 2.5 (m, 3H), 3.3 (m, 2H), 3.5 (m, 1H), 4.3 (m, 1H), 4.7 (m, 1H), 7.2 (m, 2H), 7.2 (m, 1H), 7.4 (m, 6H), 7.5 (m, 5H), 7.9 (m, 2H).

Example 91

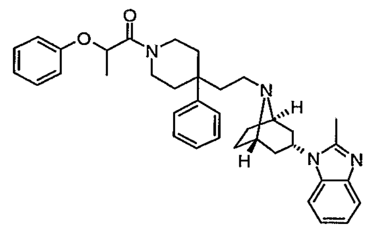
1-((1R,5S)-8-{2-[1-(2,3-dichlorobenzoyl)-4-phenyl-4-piperidinyl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1H-benzimidazole



^{1}H NMR (400 MHz, methanol-d4) δ ppm 1.8 (m, 2H), 1.9 (m, 8H), 2.1 (m, 2H), 2.3 (m, 1H), 2.5 (m, 3H), 2.5 (m, 3H), 3.2 (m, 1H), 3.4 (m, 4H), 4.2 (m, 1H), 4.8 (m, 1H), 7.2 (m, 2H), 7.3 (m, 1H), 7.4 (m, 7H), 7.5 (m, 1H), 7.6 (m, 1H).

Example 92

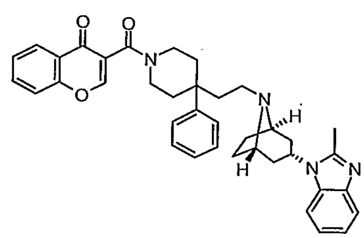
1-methyl-2-(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenyl-1-piperidinyl)-2-oxoethyl phenyl ether



[1]H NMR (400 MHz, methanol-d4) δ ppm 1.5 (dd, *J*=19.8, 6.6Hz, 3H), 1.9 (m, 13H), 2.3 (m, 2H), 2.4 (m, 2H), 2.5 (m, 3H), 3.1 (m, 1H), 3.3 (m, 2H), 3.9 (m, 2H), 4.7 (m, 1H), 5.1 (m, 1H), 6.9 (m, 3H), 7.2 (m, 5H), 7.4 (m, 5H), 7.5 (m, 1H).

Example 93

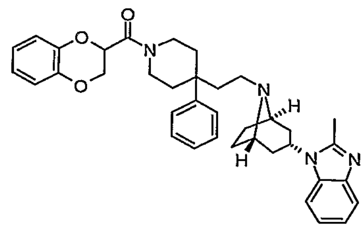
3-[(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenyl-1-piperidinyl)carbonyl]-4H-chromen-4-one



[1]H NMR (400 MHz, methanol-d4) δ ppm 1.7 (m, 2H), 1.9 (m, 8H), 2.1 (m, 2H), 2.4 (m, 4H), 2.5 (m, *J*=1.4Hz, 3H), 3.3 (m, 4H), 3.5 (m, 1H), 4.2 (s, 1H), 4.8 (m, 1H), 7.0 (m, 1H), 7.2 (m, 2H), 7.3 (m, 1H), 7.4 (m, 5H), 7.5 (m, 2H), 7.7 (d, *J*=7.8Hz, 1H), 7.8 (m, 1H), 8.2 (dd, *J*=8.2, 1.4Hz, 1H).

Example 94

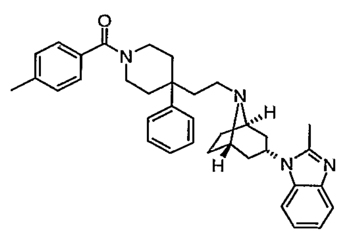
1-((1R,5S)-8-{2-[1-(2,3-dihydro-1,4-benzodioxin-2-ylcarbonyl)-4-phenyl-4-piperidinyl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1H-benzimidazole



^{1}H NMR (400 MHz, methanol-d4) δ ppm 1.7 (m, 2H) 2.0 (m, 10H) 2.3 (m, 4H) 2.6 (m, 3H) 3.1 (m, 1H) 3.4 (m, 3H) 4.0 (m, 2H) 4.2 (m, 1H) 4.4 (m, 1H) 4.8 (m, 1H) 5.1 (m, 1H) 6.8 (m, 3H) 6.9 (m, 1H) 7.2 (m, 2H) 7.3 (t, *J*=7.0Hz, 1H) 7.4 (m, 5H) 7.5 (m, 1H).

Example 96

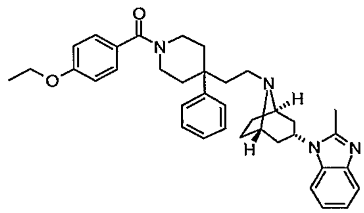
2-methyl-1-((1R,5S)-8-{2-[1-(4-methylbenzoyl)-4-phenyl-4-piperidinyl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-1H-benzimidazole



^{1}H NMR (400 MHz, methanol-d4) δ ppm 1.7 (m, 2H), 1.9 (m, 10H), 2.2 (m, 2H), 2.4 (m, 7H), 2.5 (s, 3H), 3.3 (m, 2H), 3.6 (m, 1H), 4.1 (m, 1H), 4.7 (m, 1H), 7.2 (m, 2H), 7.3 (m, 5H), 7.4 (m, 5H), 7.5 (m, 1H).

Example 97

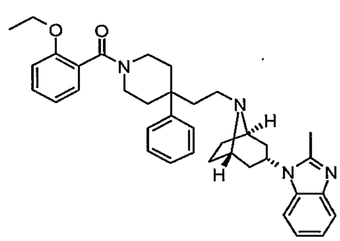
1-((1R,5S)-8-{2-[1-(4-ethoxybenzoyl)-4-phenyl-4-piperidinyl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1H-benzimidazole



^{1}H NMR (400 MHz, methanol-d4) δ ppm 1.3 (m, 1H), 1.4 (t, *J*=7.1Hz, 3H), 1.7 (m, 2H), 1.9 (m, 10H), 2.3 (m, 4H), 2.5 (m, 3H), 3.3 (m, 3H), 3.7 (m, 1H), 4.1 (m, 3H), 4.7 (m, 1H), 7.0 (m, 2H), 7.2 (m, 2H), 7.2 (m, 1H), 7.4 (m, 2H), 7.4 (m, 5H), 7.5 (m, 1H).

Example 99

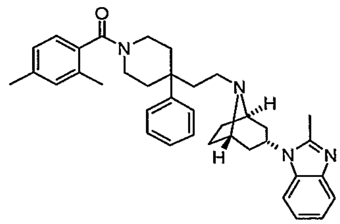
1-((1R,5S)-8-{2-[1-(2-ethoxybenzoyl)-4-phenyl-4-piperidinyl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1H-benzimidazole



^{1}H NMR (400 MHz, methanol-d4) δ ppm 1.2 (t, *J*=7.1Hz, 2H), 1.5 (t, *J*=7.0Hz, 2H), 1.9 (m, 12H), 2.3 (m, 5H), 2.5 (m, 3H), 3.2 (m, 1H), 3.4 (m, 3H), 4.0 (q, *J*=7.1Hz, 1H), 4.1 (m, 2H), 4.7 (m, 1H), 7.0 (m, 3H), 7.2 (m, 3H), 7.4 (m, 5H), 7.5 (d, *J*=7.1Hz, 1H).

Example 100

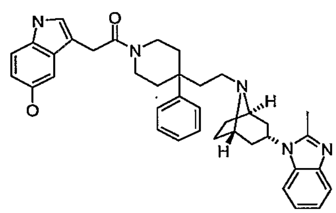
1-((1R,5S)-8-{2-[1-(2,4-dimethylbenzoyl)-4-phenyl-4-piperidinyl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1H-benzimidazole



^{1}H NMR (400 MHz, methanol-d4) δ ppm 1.9 (m, 13H), 2.2 (m, 3H), 2.3 (m, 7H), 2.5 (s, 3H), 3.1 (m, 1H), 3.4 (m, 3H), 4.1 (m, *J*=11.1, 4.6Hz, 1H), 4.7 (m, 1H), 7.1 (m, 3H), 7.2 (m, 2H), 7.2 (m, 1H), 7.4 (m, 5H), 7.5 (m, 1H).

Example 104

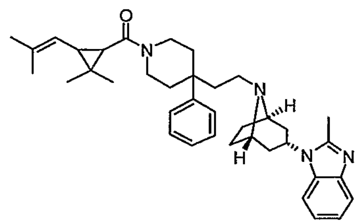
1-((1R,5S)-8-{2-[1-(2,4-dimethylbenzoyl)-4-phenyl-4-piperidinyl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1H-benzimidazole



^{1}H NMR (400 MHz, methanol-d4) δ ppm 1.3 (m, 1H), 1.7 (m, 5H), 1.9 (m, 7H), 2.2 (m, 1H), 2.4 (m, 4H), 2.5 (s, 3H), 3.1 (m, 1H), 3.2 (m, 3H), 3.8 (m, 2H), 4.1 (t, *J*=5.5Hz, 1H), 4.7 (d, *J*=8.6Hz, 1H), 6.7 (dd, *J*=8.6, 2.1Hz, 1H), 7.0 (d, *J*=2.5 Hz, 1H), 7.1 (s, 1H), 7.2 (m, 4H), 7.3 (m, 5H), 7.4 (dd, *J*=5.9, 2.7Hz, 1H), 7.5 (m, 1H).

Example 106

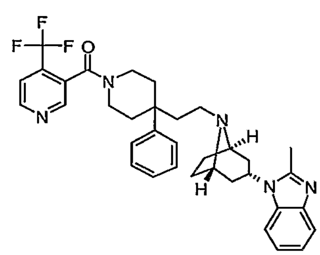
1-{(1R,5S)-8-[2-(1-{[2,2-dimethyl-3-(2-methyl-1-propenyl)cyclopropyl]carbonyl}-4-phenyl-4-piperidinyl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-2-methyl-1H-benzimidazole



^{1}H NMR (400 MHz, methanol-d4) δ ppm 1.2 (m, 3H), 1.3 (m, 2H), 1.8 (m, 20H), 2.2 (m, 3H), 2.4 (m, 3H), 2.5 (s, 3H), 3.4 (m, 1H), 3.8 (m, 2H), 4.1 (m, 1H), 4.8 (m, 1H), 4.9 (m, 1H), 5.1 (dd, *J*=35.7, 8.9Hz, 1H), 7.2 (m, 2H), 7.2 (m, 1H), 7.4 (m, 5H), 7.5 (m, 1H).

Example 107

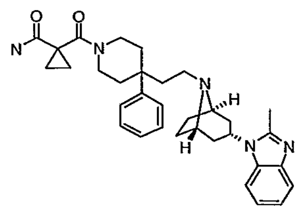
2-methyl-1-{(1R,5S)-8-[2-(4-phenyl-1-{[4-(trifluoro-methyl)-3-pyridinyl]carbonyl}-4-piperidinyl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1H-benzimidazole



^{1}H NMR (400 MHz, methanol-d4) δ ppm 1.3 (m, 1H), 1.9 (m, 12H), 2.3 (m, 1H), 2.4 (m, 4H), 2.5 (m, 3H), 3.2 (m, 1H), 3.4 (m, 2H), 4.2 (m, 1H), 4.7 (m, 1H), 7.2 (m, 2H), 7.3 (m, 1H), 7.4 (m, 5H), 7.5 (m, 1H), 7.8 (dd, *J*=13.7, 5.2Hz, 1H), 8.7 (m, *J*=72.4Hz, 1H), 8.9 (t, *J*=5.7Hz, 1H).

Example 108

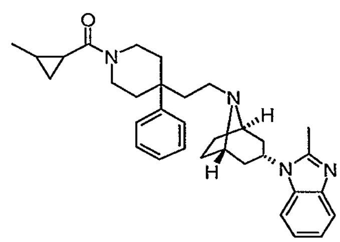
1-[(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenyl-1-piperidinyl)carbonyl]cyclopropanecarboxamide



^{1}H NMR (400 MHz, methanol-d4) δ ppm 1.3 (m, 7H), 1.7 (m, 2H), 2.0 (m, 10H), 2.4 (m, 4H), 2.5 (s, 2H), 3.3 (m, 4H), 3.8 (m, 1H), 4.1 (m, *J*=11.4, 6.1Hz, 1H), 4.7 (m, 1H), 7.2 (m, 2H), 7.2 (m, 1H), 7.4 (m, 5H), 7.5 (m, 1H).

Example 109

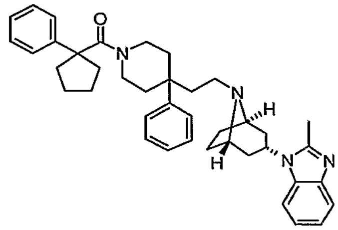
2-methyl-1-[(1R,5S)-8-(2-{1-[(2-methylcyclopropyl) carbonyl]-4-phenyl-4-piperidinyl}ethyl)-8-azabicyclo[3.2.1]oct-3-yl]-1H-benzimidazole



^{1}H NMR (400 MHz, methanol-d4) δ ppm 1.1 (m, 5H), 1.9 (m, 14H), 2.3 (m, 4H), 2.6 (m, 3H), 3.2 (m, 1H), 3.3 (m, 2H), 3.5 (m, 1H), 4.0 (m, 2H), 4.7 (m, 1H), 7.2 (m, 2H), 7.2 (m, 1H), 7.4 (m, 5H), 7.5 (m, 1H).

Example 111

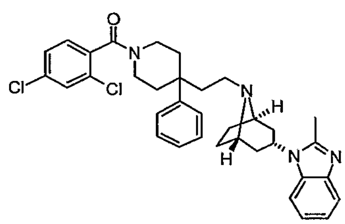
2-methyl-1-[(1R,5S)-8-(2-{4-phenyl-1-[(1-phenylcyclopentyl)carbonyl]-4-piperidinyl}ethyl)-8-azabicyclo[3.2.1]oct-3-yl]-1H-benzimidazole



^{1}H NMR (400 MHz, methanol-d4) δ ppm 1.2 (m, 1H), 1.7 (m, 10H), 2.0 (m, 7H), 2.3 (m, 6H), 2.5 (m, 3H), 2.9 (m, 1H), 3.2 (m, 3H), 3.4 (m, 1H), 4.0 (m, 1H), 4.7 (m, 1H), 7.2 (m, 7H), 7.3 (m, 5H), 7.4 (m, 1H), 7.5 (m, 1 H).

Example 113

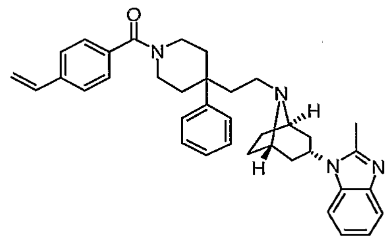
1-((1R,5S)-8-{2-[1-(2,4-dichlorobenzoyl)-4-phenyl-4-piperidinyl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1H-benzimidazole



^{1}H NMR (400 MHz, methanol-d4) δ ppm 1.7 (m, 2H), 1.9 (m, 11H), 2.3 (m, 1H), 2.4 (m, 4H), 2.5 (m, J=2.5Hz, 3H), 3.2 (m, 1H), 3.3 (m, 2H), 4.2 (m, 1H), 4.7 (m, J=10.9, 9.1Hz, 1H), 7.2 (m, 2H), 7.2 (m, 1H), 7.4 (m, 6H), 7.5 (m, 3H).

Example 117

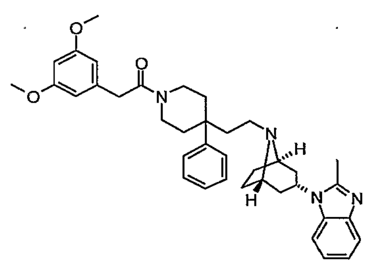
2-methyl-1-((1R,5S)-8-{2-[4-phenyl-1-(4-vinylbenzoyl)-4-piperidinyl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-1H-benzimidazole



^{1}H NMR (400 MHz, methanol-d4) δ ppm 1.7 (m, 2H), 1.9 (m, 10H), 2.2 (m, 1H), 2.4 (m, 4H), 2.5 (m, 3H), 3.3 (m, 4H), 3.6 (m, 1H), 4.1 (m, *J*=11.1, 4.3 Hz, 1H), 4.7 (m, 1H), 5.3 (d, *J*=11.1 Hz, 1H), 5.9 (d, *J*=17.5Hz, 1H), 6.8 (dd, *J*=17.7, 10.9Hz, 1H), 7.2 (m, 2H), 7.2 (m, 1H), 7.4 (d, 7H), 7.5 (m, 2H).

Example 120

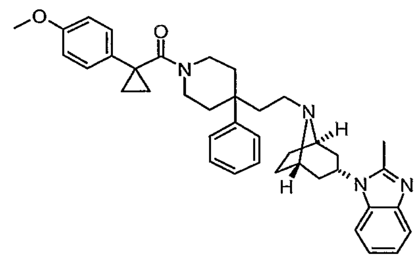
1-[(1R,5S)-8-(2-{1-[(3,5-dimethoxyphenyl)acetyl]-4-phenyl-4-piperidinyl}ethyl)-8-azabicyclo[3.2.1]oct-3-yl]-2-methyl-1H-benzimidazole



^{1}H NMR (400 MHz, methanol-d4) δ ppm 1.7 (m, 5H), 1.9 (m, 8H), 2.2 (m, 2H), 2.4 (m, 3H), 2.5 (m, 3H), 3.2 (m, 4H), 3.7 (m, 8H), 4.0 (m, 1H), 4.7 (t, 1H), 6.4 (t, *J*=2.1Hz, 1H), 6.4 (d, *J*=2.1Hz, 1H), 7.2 (m, 2H), 7.2 (m, 1H), 7.4 (m, 5H), 7.5 (m, 1H).

Example 123

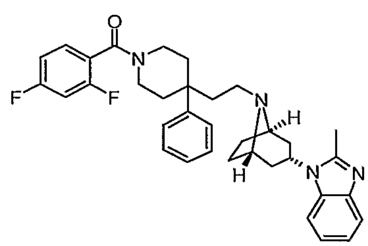
methyl 4-{1-[(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimi-dazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenyl-1-piperidinyl)carbonyl]cyclopropyl}phenyl ether



^{1}H NMR (400 MHz, methanol-d4) δ ppm 1.3 (m, 6H), 1.7 (m, 2H), 2.0 (m, 8H), 2.2 (m, 1H), 2.4 (m, 3H), 2.5 (s, 3H), 3.2 (m, 5H), 3.7 (s, 3H), 3.8 (m, 1H), 4.0 (m, 1H), 4.7 (m, 1H), 6.9 (m, 2H), 7.1 (m, 2H), 7.2 (m, 3H), 7.3 (m, 4H), 7.5 (m, 1H).

Example 127

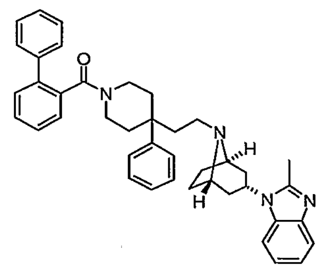
1-((1R,5S)-8-{2-[1-(2,4-difluorobenzoyl)-4-phenyl-4-piperidinyl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1H-benzimidazole



^{1}H NMR (400 MHz, methanol-d4) δ ppm 1.7 (m, 2H), 1.9 (m, 8H), 2.3 (m, 1H), 2.4 (m, 3H), 2.5 (m, 3H), 3.2 (m, 1H), 3.3 (m, 5H), 3.5 (m, 1H), 4.2 (m, 1H), 4.7 (m, 1H), 7.1 (m, *J*=9.6, 9.6Hz, 2H), 7.2 (m, 2H), 7.2 (m, 1H), 7.4 (m, 6H), 7.5 (m, 1H).

Example 128

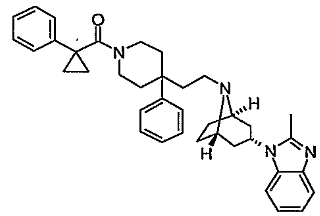
1-((1R,5S)-8-{2-[1-([1,1'-biphenyl]-2-ylcarbonyl)-4-phenyl-4-piperidinyl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1H-benzimidazole



^{1}H NMR (400 MHz, methanol-d4) δ ppm 1.5 (m, 3H), 1.9 (m, 8H), 2.2 (m, 1H), 2.4 (m, 2H), 2.5 (m, 3H), 2.8 (m, 1H), 3.0 (m, 1H), 3.2 (m, 3H), 3.4 (m, 1H), 3.8 (m, 1H), 4.2 (m, 1H), 4.7 (m, 1H), 7.4 (m, 18H).

Example 130

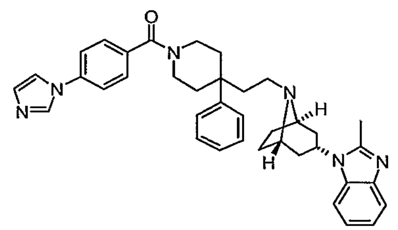
2-methyl-1-[(1R,5S)-8-(2-{4-phenyl-1-[(1-phenylcyclopropyl)carbonyl]-4-piperidinyl}ethyl)-8-azabicyclo[3.2.1]oct-3-yl]-1H-benzimidazole



^{1}H NMR (400 MHz, methanol-d4) δ ppm 1.3 (m, 5H), 1.6 (m, 2H), 1.7 (m, 3H), 1.9 (m, 8H), 2.2 (m, 1H), 2.4 (m, 2H), 2.5 (m, 3H), 3.2 (m, 3H), 3.8 (m, 1H), 4.0 (m, *J*=12.1, 5.7Hz, 1H), 4.7 (m, 1H), 7.2 (m, 6H), 7.3 (m, 6H), 7.4 (m, 1H), 7.5 (m, 1H).

Example 131

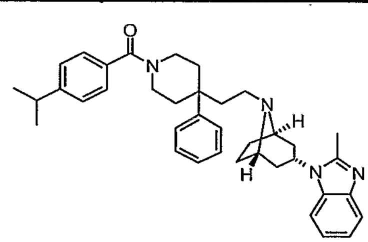
1-[(1R,5S)-8-(2-{1-[4-(1H-imidazol-1-yl)benzoyl]-4-phenyl-4-piperidinyl}ethyl)-8-azabicyclo[3.2.1]oct-3-yl]-2-methyl-1H-benzimidazole



^{1}H NMR (400 MHz, methanol-d4) δ ppm 1.7 (m, 2H), 2.0 (m, 10H), 2.3 (m, 1H), 2.4 (m, 4H), 2.5 (m, 3H), 3.4 (m, 3H), 3.6 (m, 1H), 4.2 (m, 1H), 4.7 (m, 1H), 7.2 (m, 3H), 7.2 (m, 1H), 7.4 (m, 6H), 7.5 (m, 1H), 7.6 (m, 2H), 7.6 (d, *J*=1.4 Hz, 1H), 7.7 (m, 2H).

Example 133

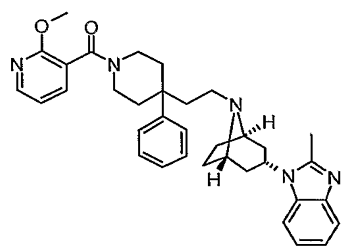
1-((1R,5S)-8-{2-[1-(4-isopropylbenzoyl)-4-phenyl-4-piperidinyl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1H-benzimidazole



^{1}H NMR (400 MHz, methanol-d4) δ ppm 1.3 (m, 6H), 1.7 (m, 2H), 1.9 (m, 10H), 2.2 (m, 1H), 2.4 (m, 3H), 2.5 (s, 3H), 2.9 (m, 1H), 3.3 (m, 4H), 3.6 (m, 1H), 4.1 (m, 1H), 4.7 (m, 1H), 7.2 (m, 2H), 7.2 (m, 1H), 7.3 (m, 3H), 7.4 (m, 6H), 7.5 (m, 1H).

Example 134

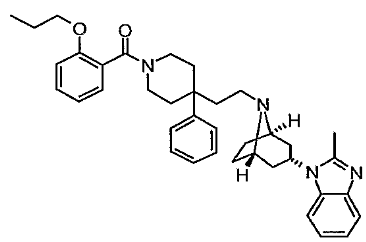
methyl 3-[(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenyl-1-piperidinyl)carbonyl]-2-pyridinyl ether



^{1}H NMR (400 MHz, methanol-d4) δ ppm 1.7 (m, *J*=7.5Hz, 2H), 1.9 (m, 10H), 2.2 (m, 1H), 2.4 (m, 3H), 2.5 (m, 3H), 3.2 (m, 1H), 3.3 (m, 4H), 3.9 (d, *J*=54.6Hz, 3H), 4.2 (m, 1H), 4.7 (m, 1H), 7.1 (m, 1H), 7.2 (m, 2H), 7.2 (d, *J*=4.6Hz, 1H), 7.4 (m, 5H), 7.5 (m, 1H), 7.6 (dd, *J*=53.7, 7.3Hz, 1H), 8.2 (dd, *J*=5.2, 2.0Hz, 1H).

Example 136

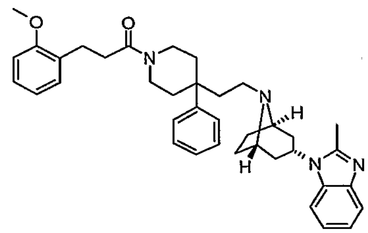
2-[(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenyl-1-piperidinyl)carbonyl]phenyl propyl ether



^{1}H NMR (400 MHz, methanol-d4) δ ppm 1.0 (m, 3H), 1.6 (m, 1H), 1.7 (m, 2H), 1.9 (m, 11H), 2.2 (m, 1H), 2.4 (m, 4H), 2.5 (d, *J*=7.1Hz, 3H), 3.2 (m, 2H), 3.4 (m, 2H), 3.9 (t, *J*=6.4Hz, 1H), 4.1 (m, 2H), 4.7 (m, 1H), 7.1 (m, 4H), 7.2 (m, 2H), 7.2 (m, 1H), 7.4 (m, 5H), 7.5 (m, 1H).

Example 138

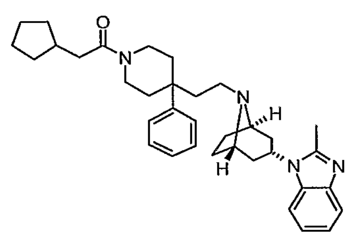
methyl 2-[3-(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenyl-1-piperidinyl)-3-oxopropyl]phenyl ether



^{1}H NMR (400 MHz, methanol-d4) δ ppm 1.5 (m, 1H), 1.7 (m, 3H), 1.8 (m, 2H), 1.9 (m, 6H), 2.1 (m, 1H), 2.2 (m, 1H), 2.4 (m, 2H), 2.5 (m, *J*=5.7Hz, 3H), 2.6 (m, 4H), 2.9 (m, 2H), 3.1 (m, 2H), 3.3 (m, 1H), 3.6 (m, 1H), 3.8 (s, 3H), 4.0 (m, 1H), 4.7 (m, 1H), 6.8 (t, *J*=7.0Hz, 1H), 6.9 (d, *J*=8.2Hz, 1H), 7.1 (dd, *J*=7.5, 1.8Hz, 1H), 7.2 (m, 2H), 7.2 (m, 1H), 7.4 (m, 5H), 7.5 (m, 1H).

Example 139

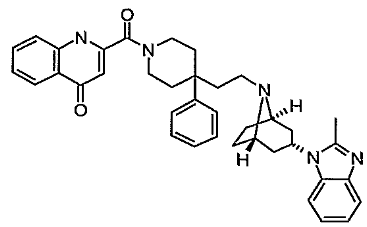
1-((1R,5S)-8-{2-[1-(cyclopentylacetyl)-4-phenyl-4-piperidinyl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1H-benzimidazole



^{1}H NMR (400 MHz, methanol-d4) δ ppm 1.2 (m, 1H), 1.6 (m, 4H), 1.9 (m, 12H), 2.2 (m, 3H), 2.4 (m, 4H), 2.6 (m, 3H), 2.8 (t, *J*=5.7Hz, 1H), 2.9 (d, *J*=2.1Hz, 1H), 3.2 (m, 1H), 3.3 (m, 3H), 3.5 (m, 1H), 3.8 (m, 1H), 4.0 (m, 1H), 4.7 (m, 1H), 7.2 (m, 2H), 7.2 (m, 1H), 7.4 (m, 5H), 7.5 (m, 1H).

Example 141

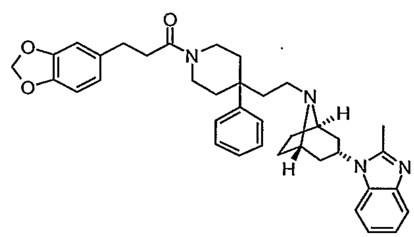
2-[(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenyl-1-piperidinyl)carbonyl]-4(1H)-quinolinone



^{1}H NMR (400 MHz, methanol-d4) δ ppm 1.7 (m, 2H), 2.0 (m, 10H), 2.4 (m, 4H), 2.5 (m, 3H), 3.3 (m, 4H), 3.6 (m, 1H), 4.2 (m, 1H), 4.7 (m, 1H), 6.3 (s, 1H), 7.2 (m, 2H), 7.3 (m, 1H), 7.4 (m, 7H), 7.5 (m, 1H), 7.6 (d, *J*=8.2Hz, 1H), 7.7 (m, 1H), 8.3 (d, *J*=7.1Hz, 1H).

Example 142

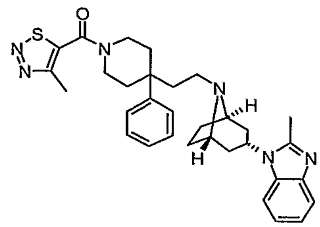
1-[(1R,5S)-8-(2-{1-[3-(1,3-benzodioxol-5-yl)propanoyl]-4-phenyl-4-piperidinyl}ethyl)-8-azabicyclo[3.2.1]oct-3-yl]-2-methyl-1H-benzimidazole



^{1}H NMR (400 MHz, methanol-d4) δ ppm 1.5 (m, 1H), 1.7 (m, 3H), 1.8 (m, 2H), 2.0 (m, 7H), 2.2 (m, 1H), 2.4 (m, 2H), 2.5 (s, 3H), 2.6 (m, 3H), 2.8 (m, 2H), 3.2 (m, 2H), 3.3 (m, *J*=3.9Hz, 1H), 3.6 (m, 1H), 3.9 (m, 1H), 4.7 (m, 1H), 5.8 (d, *J*=1.4Hz, 1H), 5.9 (s, 1H), 6.7 (m, 3H), 7.2 (m, 2H), 7.2 (m, 1H), 7.4 (m, 5H), 7.5 (m, 1H).

Example 144

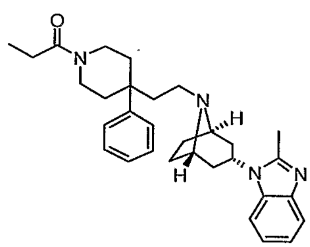
2-methyl-1-[(1R,5S)-8-(2-{1-[(4-methyl-1,2,3-thiadiazol-5-yl)carbonyl]-4-phenyl-4-piperidinyl} ethyl)-8-azabicyclo[3.2.1]oct-3-yl]-1H-benzimidazole



^{1}H NMR (400 MHz, methanol-d4) δ ppm 1.4 (m, 2H), 1.7 (m, 2H), 1.9 (m, 10H), 2.4 (m, 5H), 2.6 (m, 3H), 2.8 (m, 1H), 3.0 (m, 1H), 3.3 (m, 1H), 3.4 (m, 1H), 3.6 (m, 1H), 4.2 (m, 1H), 4.8 (m, 1H), 7.2 (m, 2H), 7.2 (m, 1H), 7.4 (m, 5H), 7.5 (m, 1H).

Example 145

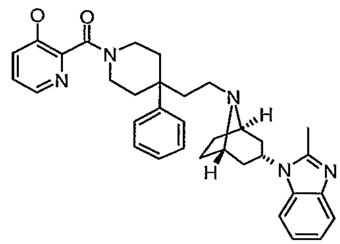
2-methyl-1-{(1R,5S)-8-[2-(4-phenyl-1-propionyl-4-piperidinyl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1H-benzimidazole



^{1}H NMR (400 MHz, methanol-d4) δ ppm 1.1 (t, J=7.5Hz, 3H), 1.7 (m, 2H), 1.9 (m, 10H), 2.3 (s, 2H), 2.4 (m, 4H), 2.5 (d, J=6.6Hz, 3H), 3.2 (m, 2H), 3.3 (m, 2H), 3.6 (m, 1H), 4.0 (m, 1H), 4.7 (m, 1H), 7.2 (m, 2H), 7.2 (m, 1H), 7.4 (m, 5H), 7.5 (m, 1H).

Example 149

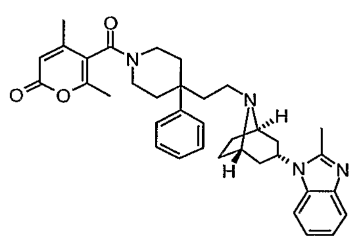
2-[(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenyl-1-piperidinyl)carbonyl]-3-pyridinol



[1]H NMR (400 MHz, methanol-d4) δ ppm 1.7 (m, 2H), 2.0 (m, 10H), 2.4 (m, 5H), 2.5 (m, 3H), 3.2 (m, 1H), 3.3 (m, 3H), 3.5 (m, 1H), 4.2 (m, *J*=4.6Hz, 1H), 4.7 (m, 1H), 7.2 (m, 2H), 7.2 (m, 1H), 7.3 (m, 2H), 7.4 (m, 5H), 7.5 (m, 1H), 8.1 (dd, *J*=3.9, 2.1Hz, 1H).

Example 150

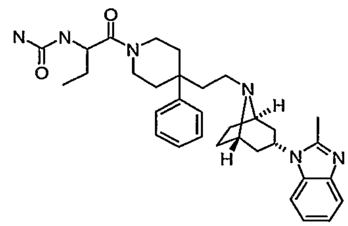
4,6-dimethyl-5-[(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenyl-1-piperidinyl)carbonyl]-2H-pyran-2-one



[1]H NMR (400 MHz, methanol-d4) δ ppm 1.6 (m, 2H), 1.9 (m, 13H), 2.1 (m, 1H), 2.2 (m, *J*=6.4Hz, 1H), 2.3 (m, 3H), 2.4 (m, 4H), 2.5 (m, *J*=1.4Hz, 3H), 2.8 (m, 1H), 3.0 (m, 1H), 3.6 (m, 1H), 4.2 (m, 1H), 4.7 (m, 1H), 6.1 (d, *J*=21.8Hz, 1H), 7.2 (m, 2H), 7.2 (m, 1H), 7.4 (m, 5H), 7.5 (m, 1H).

Example 151

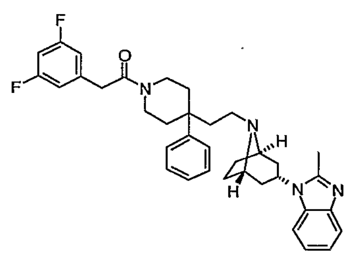
N-{1-[(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenyl-1-piperidinyl)carbonyl]propyl}urea



^{1}H NMR (400 MHz, methanol-d4) δ ppm 0.9 (m, 3H), 1.6 (m, 4H), 1.9 (m, 11H), 2.4 (m, 6), 2.5 (m, *J*=1.8Hz, 3H), 2.8 (m, 1H), 3.0 (m, 2H), 3.4 (m, 1H), 3.8 (m, 1H), 4.1 (m, 1H), 4.7 (m, 1H), 4.8 (m, 1H), 7.2 (m, 2H), 7.2 (m, 1H), 7.4 (m, 5H), 7.5 (m, 1H).

Example 154

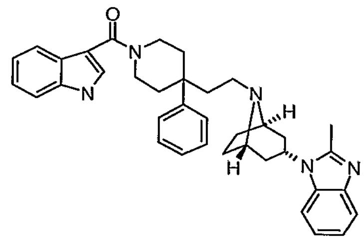
1-[(1R,5S)-8-(2-{1-[(3,5-difluorophenyl)acetyl]-4-phenyl-4-piperidinyl}ethyl)-8-azabicyclo[3.2.1]oct-3-yl]-2-methyl-1H-benzimidazole



^{1}H NMR (400 MHz, methanol-d4) δ ppm 1.8 (m, 12H), 2.3 (m, 2H), 2.4 (m, 4H), 2.5 (s, 3H), 3.2 (m, 1H), 3.3 (m, 2H), 3.8 (m, 2H), 4.0 (m, 1H), 4.7 (m, 1H), 6.8 (m, 2H), 7.2 (m, 2H), 7.2 (m, 1H), 7.4 (m, 6H), 7.5 (m, 1H).

Example 156

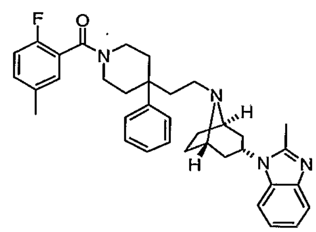
1-((1R,5S)-8-{2-[1-(1H-indol-3-ylcarbonyl)-4-phenyl-4-piperidinyl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1H-benzimidazole



^{1}H NMR (400 MHz, methanol-d4) δ ppm 1.7 (m, 2H), 1.9 (m, 10H), 2.4 (m, 7H), 2.5 (s, 3H), 2.8 (m, 1H), 3.1 (m, 1H), 3.5 (m, *J*=10.3, 10.3Hz, 1H), 4.1 (dd, *J*=11.6, 6.2Hz, 1H), 4.7 (m, 1H), 7.2 (m, 4H), 7.2 (m, 1H), 7.4 (m, 7H), 7.5 (m, 1H), 7.6 (m, 1H).

Example 157

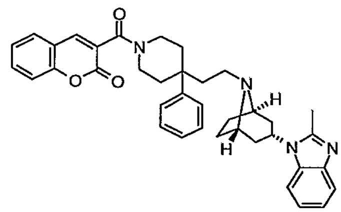
1-((1R,5S)-8-{2-[1-(2-fluoro-5-methylbenzoyl)-4-phenyl-4-piperidinyl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1H-benzimidazole



^{1}H NMR (400 MHz, methanol-d4) δ ppm 1.7 (m, 2H), 1.9 (m, 10H), 2.4 (m, 10H), 2.9 (m, 1H), 3.2 (m, 2H), 3.4 (m, 1H), 3.5 (m, 1H), 4.2 (m, 1H), 4.7 (m, 1H), 7.1 (m, 1H), 7.2 (m, 2H), 7.3 (m, 1H), 7.4 (m, 7H), 7.5 (m, 1H).

Example 158

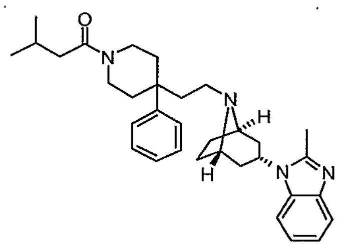
3-[(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenyl-1-piperidinyl)carbonyl]-2H-chromen-2-one



^{1}H NMR (400 MHz, methanol-d4) δ ppm 1.7 (m, 2H), 1.9 (m, 10H), 2.4 (m, 5H), 2.5 (m, 3H), 2.9 (m, 1H), 3.2 (m, 2H), 3.6 (m, 1H), 4.1 (m, 1H), 4.7 (m, 1H), 7.0 (m, 1H), 7.2 (m, 4H), 7.4 (m, 6H), 7.5 (m, *J*=6.8Hz, 1H), 7.7 (m, 1H), 8.1 (s, 1H).

Example 159

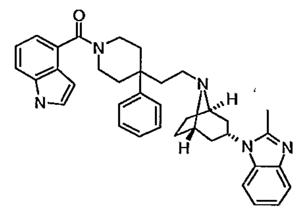
2-methyl-1-((1R,5S)-8-{2-[1-(3-methylbutanoyl)-4-phenyl-4-piperidinyl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-1H-benzimidazole



^{1}H NMR (400 MHz, methanol-d4) δ ppm 1.0 (m, 6H), 1.7 (m, 2H), 1.9 (m, 12H), 2.3 (m, 4H), 2.4 (m, 2H), 2.5 (m, *J*=6.4Hz, 3H), 3.2 (m, 1H), 3.3 (m, 2H), 3.8 (m, 1H), 4.0 (m, 1H), 4.7 (m, 1H), 7.2 (m, 2H), 7.2 (m, 1H), 7.4 (m, 5H), 7.5 (m, 1H).

Example 160

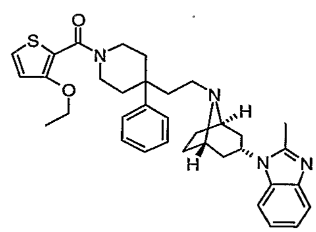
1-((1R,5S)-8-{2-[1-(1H-indol-4-ylcarbonyl)-4-phenyl-4-piperidinyl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1H-benzimidazole



^{1}H NMR (400 MHz, methanol-d4) δ ppm 1.6 (m, 2H), 1.9 (m, 13H), 2.2 (m, 1H), 2.4 (m, 5H), 3.3 (m, 2H), 3.5 (m, 2H), 4.2 (m, 1H), 4.7 (m, 1H), 6.4 (d, *J*=2.9Hz, 1H), 7.0 (d, *J*=7.1Hz, 1H), 7.2 (m, 2H), 7.2 (m, 1H), 7.3 (m, *J*=3.4, 3.4Hz, 1H), 7.4 (m, 6H), 7.5 (d, *J*=8.2Hz, 1H), 7.5 (m, 1H).

Example 162

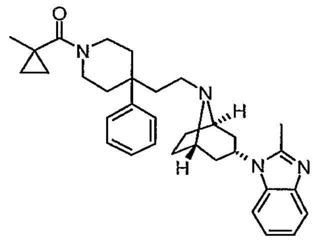
1-[(1R,5S)-8-(2-{1-[(3-ethoxy-2-thienyl)carbonyl]-4-phenyl-4-piperidinyl}ethyl)-8-azabicyclo[3.2.1]oct-3-yl]-2-methyl-1H-benzimidazole



^{1}H NMR (400 MHz, methanol-d4) δ ppm 1.4 (t, *J*=7.1Hz, 3H), 1.7 (m, 2H), 2.0 (m, 11H), 2.4 (m, 4H), 2.5 (m, 3H), 3.3 (m, 4H), 3.9 (m, 2H), 4.2 (m, 2H), 4.7 (m, 1H), 6.9 (d, *J*=5.7Hz, 1H), 7.2 (m, 2H), 7.2 (m, 1H), 7.4 (m, 5H), 7.5 (m, 1H).

Example 163

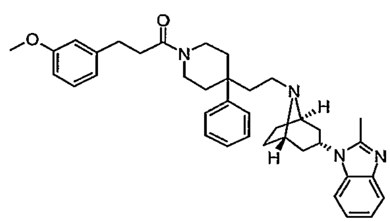
2-methyl-1-[(1R,5S)-8-(2-{1-[(1-methylcyclopropyl) carbonyl]-4-phenyl-4-piperidinyl}ethyl)-8-azabicyclo[3.2.1]oct-3-yl]-1H-benzimidazole



^{1}H NMR (400 MHz, methanol-d4) δ ppm 0.6 (d, *J*=1.4Hz, 2H), 0.9 (m, 2H), 1.3 (d, *J*=20.0Hz, 3H), 1.7 (m, 2H), 1.9 (m, 10H), 2.3 (m, 4H), 2.5 (s, 3H), 2.8 (m, 1H), 3.0 (m, 1H), 3.3 (m, 2H), 4.0 (m, 2H), 4.7 (m, 1H), 7.2 (m, 2H), 7.2 (m, 1H), 7.4 (m, 5H), 7.5 (m, 1H).

Example 164

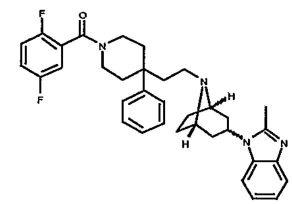
methyl 3-[3-(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenyl-1-piperidinyl)-3-oxopropyl]phenyl ether



^{1}H NMR (400 MHz, methanol-d4) δ ppm 1.4 (m, 1H), 1.7 (m, 2H), 1.8 (m, 1H), 2.0 (m, 11H), 2.2 (m, 1H), 2.4 (m, 2H), 2.5 (m, 3H), 2.7 (m, 2H), 2.9 (m, 2H), 3.1 (m, 2H), 3.6 (m, 1H), 3.7 (s, 3H), 4.0 (m, 1H), 4.7 (m, 1H), 6.7 (dd, *J*=7.8, 2.1Hz, 1H), 6.8 (m, 2H), 7.2 (m, 2H), 7.2 (m, 1H), 7.4 (m, 6H), 7.5 (m, 1H).

Example 167

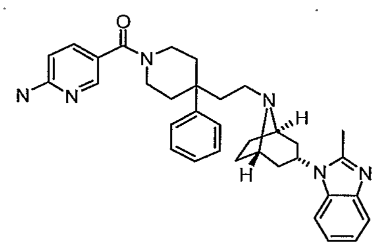
methyl 3-[3-(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenyl-1-piperidinyl)-3-oxopropyl]phenyl ether



^{1}H NMR (400 MHz, methanol-d4) δ ppm 1.7 (m, 2H), 1.9 (m, 10H), 2.3 (m, 1H), 2.4 (m, 3H), 2.5 (s, 3H), 3.2 (m, 1H), 3.3 (m, 3H), 3.5 (m, 1H), 4.2 (m, *J*=8.9, 4.6Hz, 1H), 4.7 (m, 1H), 7.2 (m, 2H), 7.2 (m, 4H), 7.4 (m, 5H), 7.5 (m, 1H).

Example 168

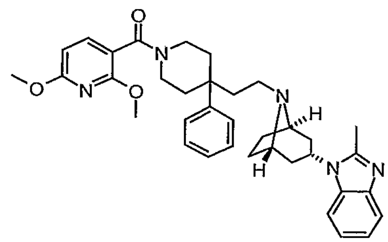
5-[(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenyl-1-piperidinyl)carbonyl]-2-pyridinylamine



^{1}H NMR (400 MHz, methanol-d4) δ ppm 1.7 (m, 2H), 2.0 (m, 10H), 2.3 (m, 5H), 2.5 (m, 3H), 2.9 (m, 2H), 3.3 (m, 3H), 3.9 (m, 2H), 4.7 (m, 1H), 6.6 (d, *J*=8.6Hz, 1H), 7.2 (m, 2H), 7.2 (m, 1H), 7.4 (m, 5H), 7.5 (m, 2H), 8.0 (d, *J*=2.1Hz, 1H).

Example 169

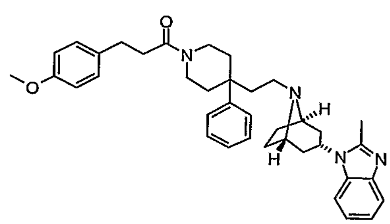
1-[(1R,5S)-8-(2-{1-[(2,6-dimethoxy-3-pyridinyl) carbonyl]-4-phenyl-4-piperidinyl}ethyl)-8-azabicyclo[3.2.1]oct-3-yl]-2-methyl-1H-benzimidazole



[1]H NMR (400 MHz, methanol-d4) δ ppm 1.7 (m, 2H), 1.9 (m, 10H), 2.2 (m, 1H), 2.4 (m, 4H), 2.5 (m, 3H), 3.2 (m, 1H), 3.3 (m, 2H), 3.4 (m, 1H), 4.0 (m, 6H), 4.1 (m, 1H), 4.7 (m, 1H), 6.4 (d, *J*=7.8Hz, 1H), 7.2 (m, 2H), 7.2 (t, *J*=6.4Hz, 1H), 7.4 (m, 5H), 7.5 (m, 2H).

Example 171

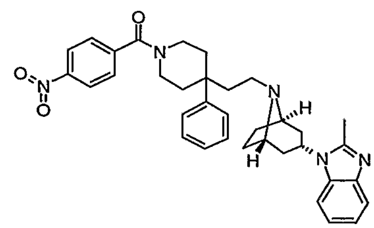
methyl 4-[3-(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenyl-1-piperidinyl)-3-oxopropyl]phenyl ether



[1]H NMR (400 MHz, methanol-d4) δ ppm 1.4 (m, 1H), 1.7 (m, 3H), 1.9 (m, 8H), 2.1 (m, 1H), 2.4 (m, 3H), 2.5 (s, 3H), 2.8 (m, 3H), 3.1 (m, 2H), 3.3 (m, 2H), 3.6 (m, 2H), 3.7 (d, *J*=12.8Hz, 3H), 3.9 (m, 1H), 4.7 (m, 1H), 6.8 (m, 2H), 7.1 (m, 2H), 7.2 (m, 2H), 7.4 (m, 6H), 7.5 (m, 1H).

Example 172

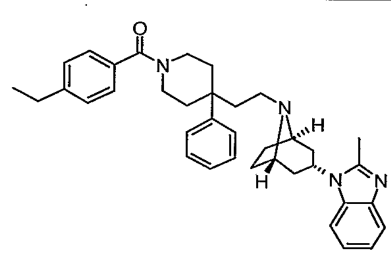
2-methyl-1-((1R,5S)-8-{2-[1-(4-nitrobenzoyl)-4-phenyl-4-piperidinyl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-1H-benzimidazole



^{1}H NMR (400 MHz, methanol-d4) δ ppm 1.7 (d, *J*=7.8Hz, 2H), 2.0 (d, *J*=12.5Hz, 8H), 2.5 (d, *J*=7.1Hz, 3H), 2.7 (s, 3H), 2.8 (m, *J*=13.6Hz, 2H), 3.1 (s, 1H), 3.3 (m, 3H), 3.5 (s, 2H), 4.2 (m, 1H), 4.8 (d, *J*=31.8Hz, 1H), 7.2 (m, 3H), 7.4 (m, 8H), 7.7 (m, 1H), 8.3 (d, *J*=8.9Hz, 1H).

Example 173

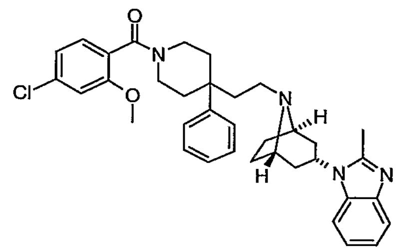
1-((1R,5S)-8-{2-[1-(4-ethylbenzoyl)-4-phenyl-4-piperidinyl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1H-benzimidazole



^{1}H NMR (400 MHz, methanol-d4) δ ppm 1.3 (m, 3H), 1.7 (m, 2H), 1.9 (m, 8H), 2.2 (m, 1H), 2.4 (m, 4H), 2.5 (s, 3H), 2.7 (m, 4H), 3.3 (m, 3H), 3.6 (m, 1H), 4.1 (m, 1H), 4.7 (m, 1H), 7.2 (m, 2H), 7.2 (m, 1H), 7.3 (m, 3H), 7.4 (m, 6H), 7.5 (m, 1H).

Example 175

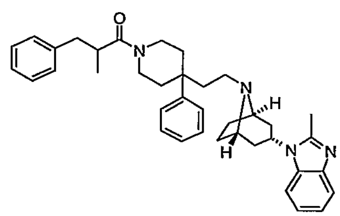
1-((1R,5S)-8-{2-[1-(4-chloro-2-methoxybenzoyl)-4-phenyl-4-piperidinyl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1H-benzimidazole



^{1}H NMR (400 MHz, methanol-d4) δ ppm 1.7 (m, 2H), 1.9 (m, 10H), 2.2 (m, 1H), 2.4 (m, 3H), 2.5 (m, 3H), 3.1 (m, 2H), 3.3 (m, 3H), 3.8 (m, *J*=57.4Hz, 3H), 4.1 (m, 1H), 4.7 (m, 1H), 7.0 (m, 1H), 7.1 (m, 2H), 7.2 (m, 2H), 7.3 (m, 1H), 7.4 (m, 5H), 7.5 (m, 1H).

Example 178

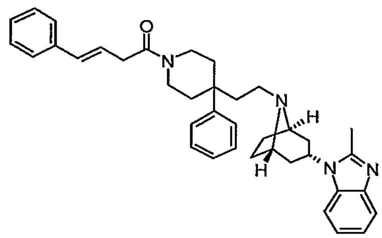
2-methyl-1-((1R,5S)-8-{2-[1-(2-methyl-3-phenylpropanoyl)-4-phenyl-4-piperidinyl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-1H-benzimidazole



^{1}H NMR (400 MHz, methanol-d4) δ ppm 1.1 (m, *J*=16.8, 6.8Hz, 3H), 1.4 (m, 1H), 1.6 (m, 4H), 1.9 (m, 8H), 2.1 (m, *J*=69.7, 13.7Hz, 2H), 2.4 (m, 3H), 2.8 (m, 3H), 3.1 (m, 1H), 3.2 (m, 2H), 3.4 (m, 1H), 3.7 (m, 2H), 4.1 (m, *J*=13.6Hz, 1H), 4.7 (m, 1H), 7.0 (m, 1H), 7.1 (m, 1H), 7.2 (m, 5H), 7.4 (m, 6H), 7.5 (m, 1H).

Example 179

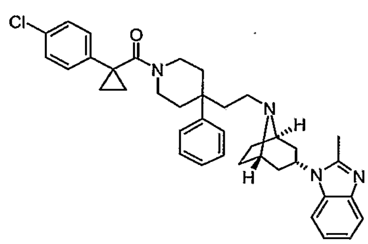
2-methyl-1-[(1R,5S)-8-(2-{4-phenyl-1-[(3E)-4-phenyl-3-butenoyl]-4-piperidinyl}ethyl)-8-azabicyclo[3.2.1]oct-3-yl]-1H-benzimidazole



^1H NMR (400 MHz, methanol-d4) δ ppm 1.7 (m, 2H), 1.9 (m, 11H), 2.4 (m, 5H), 2.5 (s, 3H), 3.2 (m, 1H), 3.4 (m, 3H), 3.8 (m, 1H), 4.0 (m, 1H), 4.7 (m, 1H), 6.3 (m, 1H), 6.5 (d, *J*=16.1Hz, 1H), 7.2 (m, 2H), 7.3 (m, 3H), 7.4 (m, 8H), 7.5 (m, 1H).

Example 181

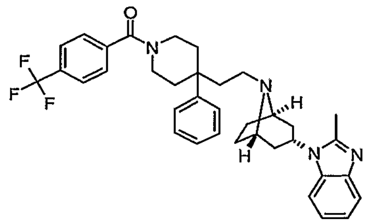
1-{(1R,5S)-8-[2-(1-{[1-(4-chlorophenyl)cyclopropyl] carbonyl}-4-phenyl-4-piperidinyl)ethyl]-8-azabicyclo [3.2.1]oct-3-yl}-2-methyl-1H-benzimidazole



^1H NMR (400 MHz, methanol-d4) δ ppm 1.4 (m, 4H), 1.7 (m, 4H), 1.9 (m, 8H), 2.1 (s, 1H), 2.3 (m, 1H), 2.4 (m, 3H), 2.5 (s, 3H), 3.2 (m, 3H), 3.8 (m, 1H), 4.0 (m, 1H), 4.7 (m, 1H), 7.2 (m, 4H), 7.4 (m, 8H), 7.5 (m, 1H).

Example 183

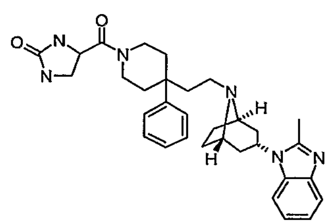
2-methyl-1-[(1R,5S)-8-(2-{4-phenyl-1-[4-(trifluoromethyl)benzoyl]-4-piperidinyl}ethyl)-8-azabicyclo[3.2.1]oct-3-yl]-1H-benzimidazole



^{1}H NMR (400 MHz, methanol-d4) δ ppm 1.7 (m, 2H), 1.9 (m, 10H), 2.2 (m, 1H), 2.4 (m, 4H), 2.5 (m, 3H), 3.3 (m, 4H), 4.2 (m, *J*=8.9, 4.6Hz, 1H), 4.7 (m, 1H), 7.2 (m, 2H), 7.2 (m, 1H), 7.4 (m, 5H), 7.5 (m, 1H), 7.6 (d, *J*=7.8Hz, 2H), 7.8 (d, *J*=7.8Hz, 2H).

Example 326A

4-[(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenyl-1-piperidinyl)carbonyl]-2-imidazolidinone



^{1}H NMR (400 MHz, methanol-d4) δ ppm 1.7 (m, 2H), 1.9 (m, 12H), 2.3 (m, 3H), 2.4 (m, 2H), 2.5 (s, 3H), 3.2 (m, 4H), 3.5 (m, 1H), 3.6 (m, 1H), 3.8 (m, 1H), 4.0 (m, 1H), 4.7 (m, 1H), 7.2 (m, 2H), 7.2 (m, 1H), 7.4 (m, 5H), 7.5 (m, 1H).

Example 326B

^{1}H NMR (300 MHz, CD_3OD) δ ppm 1.97-2.45 (m, 12H), 2.62 (s, 3H), 2.70-2.93 (m, 5H), 3.12 (m, 1H), 3.42 (m, 1H), 4.02-4.20 (m, 3H), 5.35 (m, 1H), 7.23 (m, 1H), 7.33-7.44 (m, 5H), 7.62 (m, 2H), 8.73 (m, 3H).

Example 249

^{1}H NMR (300 MHz, CD_3OD) δ 7.63-8.00 (m, 3H), 7.49-7.59 (m, 1H), 7.36-7.49 (m, 5H), 7.14-7.33 (m, 3H), 4.68-4.83 (m, 1H), 4.16-4.30 (m, 1H), 3.36-3.51 (m, 2H, under methanol), 3.11-3.28 (m, 1H), 2.56 (s, 3H), 2.34-2.51 (m, 3H), 2.23-2.34 (m, 1H), 1.85-2.01 (m, 10H), 1.59-1.77 (m, 2H), 1.18-1.38 (m, 4H).

Example 236

^{1}H NMR (300 MHz, CD_3OD) δ 7.64-7.98 (m, 3H), 7.48-7.59 (m, 1H), 7.35-7.47 (m, 5H), 7.16-7.31 (m, 3H), 4.67-4.82 (m, 1H), 4.13-4.30 (m, 1H), 3.35-3.50 (m, 4H, under methanol), 3.11-3.27 (m, 1H), 2.55 (s, 3H), 2.36-2.52 (m, 3H), 2.23-2.36 (m, 1H), 1.83-2.11 (m, 10H), 1.64-1.75 (m, 2H), 1.31 (s, 1H), 0.98-1.15 (m, 7H).

Example 21

^{1}H NMR (300 MHz, CD_3OD) δ 7.71-7.86 (m, 2H), 7.55-7.68 (m, 2H), 7.40-7.55 (m, 4H), 7.27-7.40 (m, 1H), 5.22-5.46 (m, 1H), 4.31-4.46 (d, J=12.25 Hz, 1H), 4.03-4.28 (m, 2H), 3.99 (s, 2H), 3.77-3.97 (m, 2H), 3.42-3.61 (m, 1H), 3.35 (s, 3H), 2.87-3.02 (m, 2H), 2.83 (s, 3H), 2.66-2.79 (m, 2H), 2.33-2.52 (m, 3H), 2.10-2.33 (m, 7H), 1.72-2.08 (m, 2H), 1.40 (s, 1H), 1.19-1.36 (m, 5H).

Example 252

^{1}H NMR (300 MHz, CD_3OD) δ 7.49-7.59 (m, 1H), 7.33-7.49 (m, 5H), 7.12-7.31 (m, 3H), 4.67-4.84 (m, 1H), 3.97-4.12 (m, 1H), 3.76-3.89 (m, 1H), 3.34-3.40 (m, 1H, under methanol), 3.12-3.26 (m, 1H), 2.65 (s, 3H), 2.51-2.61 (m, 5H), 2.36-2.51 (m, 2H), 2.22-2.36 (m, 2H), 1.74-2.12 (m, 10H), 1.61-1.74 (m, 2H), 1.21-1.32 (d, J=1.69 Hz, 6H).

Example 253

^{1}H NMR (300 MHz, CD_3OD) δ 7.48-7.61 (m, 1H), 7.14-7.48 (m, 13H), 5.03-5.15 (m, 1H), 4.66-4.82 (m, 1H), 3.91-4.09 (m, 1H), 3.57-3.77 (m, 1H),

3.00-3.29 (m, 2H), 2.71-2.95 (m, 2H), 2.62-2.71 (m, 6H), 2.57 (s, 3H), 2.32-2.51 (m, 2H), 2.08-2.30 (m, 1H), 1.60-2.08 (m, 10H).

Example 254

^{1}H NMR (300 MHz, CD_3OD) δ 7.50-7.59 (m, 1H), 7.34-7.50 (m, 5H), 7.14-7.31 (m, 3H), 4.67-4.83 (m, 1H), 4.33-4.52 (bs, 1H), 3.92-4.15 (bs, 1H), 3.48-3.70 (bs, 1H), 3.08-3.27 (bs, 1H), 2.62-2.70 (m, 6H), 2.51-2.62 (m, 3H), 2.35 (s, 3H), 1.78-2.08 (m, 8H), 1.55-1.73 (m, 4H).

Example 255

^{1}H NMR (300 MHz, CD_3OD) δ 7.32-7.60 (m, 6H), 7.11-7.32 (m, 3H), 4.69-4.84 (m, 1H), 3.34-3.41 (m, 2H, under methanol), 2.66 (s, 1H), 2.56 (s, 3H), 2.36-2.52 (m, 2H), 2.21-2.35 (m, 2H), 1.49-2.21 (m, 18H).

Example 256

^{1}H NMR (300 MHz, CD_3OD) δ 7.33-7.59 (m, 6H), 7.12-7.31 (m, 3H), 4.71-4.85 (m, 1H), 3.84-4.15 (m, 1H), 3.34-3.50 (m, 2H, under methanol), 2.63-2.75 (m, 7H), 2.56 (s, 3H), 2.35-2.52 (m, 2H), 2.20-2.35 (m, 2H), 1.49-2.10 (m, 17H), 1.28 (s, 2H).

Example 257

^{1}H NMR (300 MHz, CD_3OD) δ 7.33-7.59 (m, 6H), 7.13-7.31 (m, 3H), 4.66-4.85 (m, 1H), 4.13-4.25 (m, 1H), 3.94-4.13 (m, 1H), 3.71-3.86 (m, 1H), 3.35-3.41 (m, 1H, under methanol), 3.09-3.27 (m, 1H), 2.64-2.71 (m, 5H), 2.53-2.64 (m, 4H), 2.20-2.53 (m, 5H), 1.74-2.12 (m, 8H), 1.63-1.74 (m, 2H), 1.18-1.27 (m, 3H).

Example 258

^{1}H NMR (300 MHz, CD_3OD) δ 7.35-7.59 (m, 6H), 7.13-7.32 (m, 3H), 4.67-4.85 (m, 1H), 3.98-4.32 (m, 1H), 3.35-3.63 (m, 1H, under methanol), 2.66 (s, 6H), 2.56 (s, 3H), 2.36-2.52 (m, 2H), 2.24-2.36 (m, 2H), 1.77-2.09 (m, 10H), 1.60-1.77 (m, 4H), 1.30 (s, 1H), 0.77-0.96 (t, J=7.26 Hz, 6H).

Example 260

^{1}H NMR (300 MHz, CD_3OD) δ 7.50-7.61 (m, 1H), 7.13-7.50 (m, 13H), 4.62-4.81 (m, 1H), 3.89-4.13 (m, 1H), 3.69-3.89 (m, 1H), 3.12-3.31 (m, 2H), 2.62-2.71 (m, 7H), 2.56 (s, 3H), 2.28-2.47 (m, 2H), 2.06-2.27 (m, 1H), 1.73-2.03 (m, 5H), 1.51-1.73 (m, 7H).

Example 262

^{1}H NMR (300 MHz, CD_3OD) δ 7.50-7.61 (m, 1H), 7.15-7.50 (m, 17H), 4.71-4.84 (m, 1H), 4.48 (s, 2H), 4.06-4.24 (m, 1H), 3.58-3.75 (m, 1H), 3.35-3.52 (m, 2H), 2.59-2.80 (m, 9H), 2.50 (s, 4H), 2.09-2.21 (m, 2H), 1.90-2.08 (m, 5H), 1.71-1.83 (m, 2H).

Example 263

^{1}H NMR (300 MHz, CD_3OD) δ 7.51-7.60 (m, 1H), 7.10-7.51 (m, 13H), 4.61-4.79 (m, 1H), 3.38-4.14 (m, 1H), 3.68-3.88 (m, 1H), 3.14-3.29 (m, 2H), 2.58-2.72 (m, 8H), 2.53 (s, 3H), 2.28-2.48 (m, 2H), 2.06-2.28 (m, 1H), 1.75-2.03 (m, 5H), 1.55-1.73 (m, 6H).

Example 264

^{1}H NMR (300 MHz, CD_3OD) δ 7.73-7.96 (dd, 1H, J=43.02, 7.44), 7.49-7.68 (m, 2H), 7.34-7.48 (m, 5H), 7.12-7.34 (m, 3H), 4.67-4.83 (m, 1H), 4.12-4.31 (m, 1H), 3.34-3.44 (m, 3H, under methanol), 3.12-3.28 (m, 1H), 2.56 (s, 3H), 2.35-2.52 (m, 3H), 2.23-2.35 (m, 1H), 1.83-2.12 (m, 11H), 1.62-1.78 (m, 2H), 1.10-1.21 (d, *J*=6.23 Hz, 2H).

Example 265

^{1}H NMR (300 MHz, CD_3OD) δ 7.985-8.04 (m, 2H), 7.62-7.77 (m, 2H), 7.49-7.61 (m, 1H), 7.33-7.48 (m, 5H), 7.12-7.33 (m, 3H), 4.66-4.84 (m, 1H), 4.09-4.27 (m, 1H), 3.64-3.80 (t, *J*=5.8 Hz, 4H), 3.46-3.64 (m, 1H), 2.61-2.73 (m, 7H), 2.51-2.60 (m, 3H), 2.35-2.50 (m, 3H), 2.19-2.35 (m, 1H), 1.79-2.15 (m, 9H), 1.57-1.79 (m, 3H), 1.19-1.41 (m, 3H).

Example 235

^1H NMR (300 MHz, CD_3OD) δ 7.67-7.94 (m, 3H), 7.48-7.60 (m, 1H), 7.34-7.48 (m, 5H), 7.13-7.33 (m, 3H), 4.66-4.83 (m, 1H), 4.16-4.29 (m, 1H), 3.33-3.49 (m, 4H, under methanol), 3.12-3.28 (m, 1H), 2.57-2.61 (m, 1H), 2.51-2.57 (m, 4H), 2.36-2.51 (m, 3H), 2.23-2.36 (m, 1H), 1.83-2.09 (m, 12H), 1.61-1.76 (m, 2H).

Example 237

^1H NMR (300 MHz, CD_3OD) δ 7.66-7.94 (m, 3H), 7.48-7.58 (m, 1H), 7.35-7.48 (m, 5H), 7.13-7.33 (m, 3H), 4.68-4.83 (m, 1H), 4.15-4.29 (m, 1H), 3.34-3.46 (m, 6H, under methanol), 3.16-3.28 (m, 4H), 3.02-3.14 (m, 2H), 2.55 (s, 3H), 2.35-2.50 (m, 3H), 2.24-2.35 (m, 1H), 1.83-2.13 (m, 11H), 1.63-1.77 (m, 2H).

Example 288

^1H NMR (300 MHz, CD_3OD) δ 7.67-7.94 (m, 3H), 7.51-7.59 (m, 1H), 7.38-7.51 (m, 2H), 7.16-7.30 (m, 4H), 6.97-7.08 (m, 1H), 4.68-4.82 (m, 1H), 4.13-4.29 (m, 1H), 3.35-3.54 (m, 3H, under methanol), 2.40-2.81 (m, 12H), 1.86-2.16 (m, 9H), 1.67-1.80 (m, 2H), 1.23-1.33 (m, 2H).

Example 364

^1H NMR (300 MHz, CD_3OD) δ 7.65-7.97 (m, 3H), 7.51-7.62 (m, 1H), 7.38-7.51 (m, 2H), 7.13-7.32 (m, 4H), 6.94-7.12 (m, 1H), 4.68-4.82 (m, 1H), 4.08-4.30 (m, 1H), 3.34-3.65 (m, 4H, under methanol), 2.84-3.06 (m, 2H), 2.67 (s, 3H), 2.44-2.61 (m, 4H), 2.32-2.44 (m, 1H), 2.16-2.32 (m, 2H), 1.77-2.16 (m, 9H), 1.27-1.39 (m, 2H), 1.00-1.17 (m, 3H).

Example 291

^1H NMR (300 MHz, CD_3OD) δ 7.68-7.96 (m, 3H), 7.50-7.59 (m, 1H), 7.38-7.50 (m, 2H), 7.14-7.33 (m, 4H), 6.95-7.11 (m, 1H), 4.68-4.83 (m, 1H), 4.08-4.32 (m, 1H), 3.34-3.61 (m, 5H, under methanol), 2.61-2.71 (m, 4H),

2.57 (s, 3H), 2.08-2.31 (m, 2H), 1.84-2.08 (m, 7H), 1.69-1.84 (m, 1H), 1.30 (s, 4H), 0.39-0.67 (m, 4H).

Example 292

^{1}H NMR (300 MHz, CD_3OD) δ 7.64-7.98 (m, 3H), 7.50-7.58 (m, 1H), 7.37-7.50 (m, 2H), 7.11-7.31 (m, 4H), 6.95-7.09 (m, 1H), 4.65-4.81 (m, 1H), 4.09-4.27 (m, 1H), 3.36-3.56 (m, 4H, under methanol), 3.08-3.26 (m, 1H), 2.57 (s, 3H), 2.31-2.51 (m, 4H), 2.16-2.31 (m, 1H), 1.78-2.13 (m, 11H), 1.64-1.78 (m, 2H), 0.96-1.11 (m, 6H).

Example 308

^{1}H NMR (300 MHz, CD_3OD) δ 7.63-7.93 (m, 3H), 7.49-7.59 (m, 1H), 7.38-7.48 (m, 1H), 7.13-7.35 (m, 5H), 7.03-7.13 (m, 1H), 4.67-4.83 (m, 1H), 4.15-4.29 (m, 1H), 3.34-3.41 (m, 5H, under methanol), 3.12-3.29 (m, 1H), 2.52-2.61 (m, 6H), 2.40-2.52 (m, 3H), 2.34-2.40 (m, 4H), 2.19-2.34 (m, 1H), 1.83-2.11 (m, 9H), 1.63-1.75 (m, 2H).

Example 309

^{1}H NMR (300 MHz, CD_3OD) δ 7.71-7.93 (m, 3H), 7.53-7.59 (m, 1H), 7.40-7.49 (m, 2H), 7.17-7.29 (m, 4H), 6.97-7.08 (m, 1H), 4.11-4.28 (m, 1H), 3.48-3.61 (m, 1H), 3.34-3.48 (m, 3H, under methanol), 3.12-3.30 (m, 1H), 2.84-3.03 (m, 2H), 2.67 (s, 3H), 2.49-2.62 (m, 3H), 2.31-2.46 (m, 1H), 2.16-2.31 (m, 2H), 1.80-2.15 (m, 9H), 1.27-1.41 (m, 3H), 1.01-1.13 (m, 3H).

Example 310

^{1}H NMR (300 MHz, CD_3OD) δ 7.67-7.93 (m, 3H), 7.51-7.57 (m, 1H), 7.40-7.45 (m, 1H), 7.17-7.33 (m, 5H), 7.05-7.12 (m, 1H), 4.69-4.84 (m, 1H), 4.11-4.31 (m, 1H), 3.35-3.48 (m, 2H, under methanol), 3.13-3.28 (m, 1H), 2.79-2.94 (m, 2H), 2.67 (s, 3H), 2.57 (s, 2H), 2.41-2.53 (m, 2H), 2.33-2.41 (m, 3H), 2.20-2.33 (m, 1H), 1.82-2.11 (m, 9H), 1.63-1.77 (m, 2H), 1.39-1.57 (m, 2H), 0.80-0.96 (m, 3H).

Example 311

^{1}H NMR (300 MHz, CD_3OD) δ 7.68-7.97 (m, 3H), 7.50-7.59 (m, 1H), 7.38-7.48 (m, 1H), 7.15-7.36 (m, 5H), 7.04-7.15 (m, 1H), 4.69-4.83 (m, 1H), 4.14-4.34 (m, 1H), 3.34-3.48 (m, 2H, under methanol), 3.13-3.26 (m, 1H), 2.67 (s, 2H), 2.57 (s, 3H), 2.42-2.51 (m, 2H), 2.33-2.42 (m, 3H), 2.13-2.33 (m, 2H), 1.81-2.13 (m, 9H), 1.66-1.79 (d, J= 7.76 Hz, 2H), 1.31 (s, 3H), 0.44-0.65 (m, 4H).

Example 312

^{1}H NMR (300 MHz, CD_3OD) δ 7.66-7.94 (m, 3H), 7.51-7.56 (m, 1H), 7.39-7.45 (m, 1H), 7.16-7.33 (m, 5H), 7.05-7.13 (m, 1H), 4.72-4.83 (m, 1H), 4.13-4.31 (m, 1H), 3.35-3.49 (m, 3H, under methanol), 3.10-3.27 (m, 1H), 2.68 (s, 2H), 2.55 (s, 3H), 2.34-2.51 (m, 6H), 2.20-2.34 (m, 1H), 1.85-2.12 (m, 10H), 1.65-1.77 (m, 2H), 1.31 (s, 1H), 0.97-1.12 (m, 6H).

Example 293

^{1}H NMR (300 MHz, CD_3OD) δ 8.08 (s, 1H), 7.61-7.76 (m, 2H), 7.50-7.58 (m, 1H), 7.36-7.49 (m, 2H), 7.13-7.31 (m, 4H), 6.94-7.07 (m, 1H), 4.68-4.82 (m, 1H), 4.08-4.22 (m, 1H), 3.52-3.67 (m, 1H), 3.35-3.51 (m, 4H, under methanol), 2.52-2.62 (m, 6H), 2.34-2.52 (m, 3H), 2.17-2.30 (m, 1H), 1.81-2.14 (m, 11H), 1.64-1.77 (m, 2H).

Example 273

^{1}H NMR (300 MHz, CD_3OD) δ 7.66-7.94 (m, 3H), 7.49-7.57 (m, 1H), 7.35-7.49 (m, 5H), 7.23-7.33 (m, 1H), 7.14-7.23 (m, 2H), 4.67-4.83 (m, 1H), 4.16-4.30 (m, 1H), 3.34-3.43 (m, 4H, under methanol), 3.11-3.26 (m, 1H), 2.86-3.03 (m, 2H), 2.55 (s, 3H), 2.36-2.52 (m, 3H), 2.22-2.36 (m, 1H), 1.86-2.11 (m, 11H), 1.64-1.76 (m, 2H), 1.01-1.14 (dd, J=16.03, 7.5 Hz, 3H,).

Example 274

^{1}H NMR (300 MHz, CD_3OD) δ 7.65-7.94 (m, 3H), 7.48-7.60 (m, 1H), 7.35-7.48 (m, 5H), 7.23-7.30 (m, 1H), 7.15-7.23 (m, 2H), 4.66-4.82 (m, 1H),

4.16-4.27 (m, 1H), 3.34-3.46 (m, 4H, under methanol), 3.10-3.27 (m, 1H), 2.77-2.92 (m, 2H), 2.55 (s, 3H), 2.35-2.51 (m, 3H), 2.21-2.35 (m, 1H), 1.84-2.09 (m, 11H), 1.61-1.75 (m, 2H), 1.37-1.56 (m, 2H), 0.81-0.94 (dd, J=16.10, 7.48 Hz, 3H).

Example 275

^{1}H NMR (300 MHz, CD_3OD) δ 7.68-7.98 (m, 3H), 7.48-7.60 (m, 1H), 7.35-7.48 (m, 5H), 7.24-7.35 (m, 1H), 7.14-7.24 (m, 2H), 4.66-4.82 (m, 1H), 4.16-4.30 (m, 1H), 3.34-3.43 (m, 6H, under methanol), 2.55 (s, 3H), 2.35-2.51 (m, 2H), 2.13-2.35 (m, 2H), 1.83-2.12 (m, 9H), 1.65-1.76 (m, 2H), 1.30 (s, 2 H), 0.41-0.61 (m, 3H).

Example 210

^{1}H NMR (300 MHz, CD_3OD) δ 7.91-8.00 (m, 1H), 7.87 (s, 1H), 7.64-7.74 (m, 2H), 7.50-7.58 (m, 1H), 7.36-7.49 (m, 5H), 7.22-7.32 (m, 1H), 7.14-7.22 (m, 2H), 4.69-4.82 (m, 1H), 4.09-4.30 (m, 1H), 3.47-3.66 (m, 1H), 3.34-3.39 (m, 3H, under methanol), 2.50-2.59 (m, 6H), 2.36-2.50 (m, 3H), 2.22-2.35 (m, 1H), 1.83-2.11 (m, 10H), 1.65-1.76 (m, 2H), 1.30 (s, 2 H).

Example 294

^{1}H NMR (300 MHz, CD_3OD) δ 7.74-7.96 (dd, J=38.00, 7.77 Hz, 1H), 7.49-7.68 (m, 2H), 7.35-7.49 (m, 2H), 7.12-7.32 (m, 4H), 6.94-7.09 (m, 1H), 4.66-4.83 (m, 1H), 4.12-4.25 (m, 1H), 3.34-3.54 (m, 3H, under methanol), 3.13-3.28 (m, 1H), 2.56 (s, 3H), 2.30-2.52 (m, 3H), 2.16-2.30 (m, 1H), 1.79-2.09 (m, 9H), 1.64-1.78 (m, 2H), 1.26-1.39 (m, 1H), 1.09-1.19 (d, J=6.13 Hz, 3H).

Example 295

^{1}H NMR (300 MHz, CD_3OD) δ 7.99-8.10 (m, 1H), 7.86-7.99 (m, 1H), 7.50-7.59 (m, 1H), 7.36-7.50 (m, 3H), 7.13-7.30 (m, 4H), 6.95-7.07 (m, 1H), 4.67-4.83 (m, 1H), 4.13-4.25 (m, 1H), 3.42-3.59 (m, 1H), 3.34-3.41 (m, 2H, under methanol), 2.56 (s, 3H), 2.30-2.50 (m, 3H), 2.18-2.30 (m, 1H), 1.80-

2.12 (m, 10H), 1.65-1.80 (m, 2H), 1.22-1.42 (m, 1H), 1.09-1.19 (d, *J*=6.23 Hz, 3H).

Example 296

^{1}H NMR (300 MHz, CD_3OD) δ 7.89-8.00 (m, 1H), 7.61-7.88 (m, 2H), 7.50-7.60 (m, 1H), 7.34-7.50 (m, 2H), 7.12-7.34 (m, 4H), 6.94-7.07 (m, 1H), 4.64-4.83 (m, 1H), 4.10-4.27 (m, 1H), 3.34-3.54 (m, 3H, under methanol), 3.12-3.27 (m, 1H), 2.56 (s, 3H), 2.30-2.51 (m, 3H), 2.16-2.30 (m, 1H), 1.79-2.12 (m, 11H), 1.63-1.79 (m, 2H), 1.23-1.36 (m, 2H).

Example 297

^{1}H NMR (300 MHz, CD_3OD) δ 7.98-8.04 (m, 1H), 7.87-7.96 (m, 1H), 7.50-7.57 (m, 1H), 7.38-7.48 (m, 3H), 7.15-7.28 (m, 4H), 6.96-7.05 (m, 1H), 4.66-4.83 (m, 1H), 4.13-4.24 (m, 1H), 3.64-3.76 (m, 2H), 3.41-3.54 (m, 2H), 3.30-3.34 (m, 3H), 3.18-3.29 (m, 1H), 2.543 (s, 3H), 2.30-2.51 (m, 3H), 2.15-2.29 (m, 1H), 1.84-2.09 (m, 9H), 1.66-1.76 (m, 2H), 1.27-1.32 (m, 1H).

Example 298

^{1}H NMR (300 MHz, CD_3OD) δ 7.67-7.95 (m, 3H), 7.50-7.58 (m, 1H), 7.39-7.46 (m, 2H), 7.15-7.27 (m, 4H), 6.96-7.06 (m, 1H), 4.65-4.83 (m, 1H), 4.11-4.26 (m, 1H), 3.63-3.80 (m, 2H), 3.37-3.54 (m, 2H), 3.29-3.34 (m, 3H), 3.11-3.27 (m, 1H), 2.54 (s, 3H), 2.31-2.51 (m, 3H), 2.17-2.29 (m, 1H), 1.86-2.09 (m, 9H), 1.64-1.77 (m, 2H), 1.27-1.33 (m, 1H).

Example 315

^{1}H NMR (300 MHz, CD_3OD) δ 7.64-7.97 (m, 3H), 7.50-7.56 (m, 1H), 7.38-7.45 (m, 1H), 7.14-7.33 (m, 5H), 7.04-7.12 (m, 1H), 4.67-4.83 (m, 1H), 4.16-4.27 (m, 1H), 3.37-3.46 (m, 1H), 3.30-3.34 (m, 5H), 3.11-3.27 (m, 1H), 2.54 (s, 3H), 2.41-2.51 (m, 2H), 2.33-2.40 (m, 3H), 2.22-2.32 (m, 1H), 1.81-2.10 (m, 10H), 1.64-1.74 (m, 2H), 1.27-1.35 (m, 1H).

Example 278

^{1}H NMR (300 MHz, CD_3OD) δ 8.00-8.08 (m, 1H), 7.85-7.98 (br.s, 1H), 7.50-7.58 (m, 1H), 7.36-7.46 (m, 1H), 7.36-7.46 (m, 6H), 7.23-7.32 (m, 1H), 7.14-7.22 (m, 2H), 4.67-4.83 (m, 1H), 4.15-4.28 (m, 1H), 3.18-3.58 (m, 7H), 2.51-2.57 (m, 3H), 2.34-2.50 (m, 3H), 1.81-2.09 (m, 10H), 1.62-1.75 (m, 2H), 1.26-1.33 (m, 1H).

Example 279

^{1}H NMR (300 MHz, CD_3OD) δ 7.94-8.01 (m, 1H), 7.79-7.92 (m, 1H), 7.51-7.57 (m, 1H), 7.37-7.47 (m, 6H), 7.23-7.31 (m, 1H), 7.16-7.22 (m, 2H), 4.68-4.81 (m, 1H), 4.16-4.29 (m, 1H), 3.42-3.59 (m, 2H), 3.20-3.41 (m, 7H), 2.52-2.60 (m,4H), 2.25-2.49 (m, 3H), 1.85-2.09 (m, 8H), 1.66-1.75 (m, 1H), 1.28-1.34 (s, 2H).

Example 280

^{1}H NMR (300 MHz, CD_3OD) δ 7.95-8.02 (m, 1H), 7.82-7.93 (m, 1H), 7.51-7.56 (m, 1H) 7.37-7.47 (m, 6H), 7.23-7.30 (m, 1H), 7.15-7.23 (m, 2H), 4.66-4.83 (m, 1H), 4.15-4.29 (m, 1H), 3.17-3.58 (m, 8H), 2.86-2.99 (q, 2H), 2.52-2.56 (s, 3H), 2.35-2.50 (m, 3H), 1.81-2.10 (m, 8H), 1.63-1.74 (q, 2H), 1.27-1.34 (s, 1H), 1.01-1.13 (t, 3H).

Example 281

^{1}H NMR (300 MHz, CD_3OD) δ 7.95-8.02 (m, 1H), 7.83-7.94 (br s, 1H), 7.50-7.57 (m, 1H), 7.37-7.48 (m, 6H), 7.23-7.30 (m, 1H), 7.15-7.23 (m, 2H), 4.67-4.83 (m, 1H), 4.16-4.27 (m, 1H), 3.30-3.33(m, 4H), 2.80-2.89 (m, 2H), 2.54 (s, 3H), 2.35-2.51 (m, 3H), 2.24-2.34 (m, 1H), 1.84-2.11 (m, 8H), 1.65-1.76 (m, 2H), 1.40-1.55 (m, 2H), 1.30 (s, 2H), 0.88 (t, J=7.4Hz, 3H).

Example 282

^{1}H NMR (300 MHz, CD_3OD) δ 7.98-8.05 (m, 1H), 7.85-7.96 (m, 1H), 7.50-7.57 (m, 1H), 7.37-7.50 (m, 6H), 7.22-7.32 (m, 1H), 7.15-7.22 (m, 2H), 4.67-4.83 (m, 1H), 4.16-4.29 (m, 1H), 3.37-3.59 (m, 2H), 3.29-3.34 (m, 4H),

2.54 (s, 3H), 2.36-2.51 (m, 3H), 2.17-2.35 (m, 2H), 1.82-2.10 (m, 8H), 1.64-1.75 (m, 2H), 1.31 (s, 2H), 0.44-0.62 (m, 4H).

Example 283

^{1}H NMR (300 MHz, CD_3OD) δ 7.96-8.03 (m, 1H), 7.84-7.95 (m, 1H), 7.50-7.57 (m, 1H), 7.37-7.47 (m, 6H), 7.22-7.30 (m, 1H), 7.15-7.22 (m, 2H), 4.68-4.83 (m, 1H), 4.16-4.28 (m, 1H), 3.18-3.53 (m, 7H), 2.54 (s, 3H), 2.35-2.51 (m, 3H), 2.24-2.35 (m, 1H), 1.84-2.09 (m, 8H), 1.65-1.75 (m, 2H), 1.28-1.32 (m, 2H), 1.01-1.09 (d, J=6.4Hz, 6H).

Example 303

^{1}H NMR (300 MHz, CD_3OD) δ 7.95-8.02 (m, 1H), 7.84-7.94 (m, 1H), 7.50-7.57 (m, 1H), 7.37-7.48 (m, 3H), 7.25-7.28 (m, 1H), 7.14-7.25 (m, 4H), 6.96-7.05 (m, 1H), 4.66-4.82 (m, 1H), 4.12-4.24 (m, 1H), 3.18-3.56 (m, 6H), 2.88-2.98 (q, J=7.3Hz, 2H), 2.4 (s, 3H), 2.31-2.51 (m, 3H), 2.18-2.29 (m, 1H), 1.83-2.09 (m, 8H), 1.65-1.76 (m, 2H), 1.28-1.32 (m, 1H), 1.08 (t, J=7.3Hz, 3H).

Example 304

^{1}H NMR (300 MHz, CD_3OD) δ 7.95-8.02 (m, 1H), 7.83-7.93 (m, 1H), 7.51-7.57 (m, 1H), 7.38-7.48 (m, 3H), 7.26-7.29 (m, 1H), 7.16-7.26 (m, 3H), 6.97-7.07 (m, 1H), 4.68-4.83 (m, 1H), 4.10-4.24 (m, 1H), 3.37-3.54 (m, 1H), 3.30-3.54 (m, 4H), 2.80-2.88 (t, J=7.0Hz, 2H), 2.54 (s, 3H), 2.31-2.50 (m, 3H), 2.17-2.30 (m, 1H), 1.83-2.11 (m, 8H), 1.68-1.77 (m, 2H), 1.41-1.55 (m, 2H), 1.30 (m, 3H), 0.88 (t, J=7.0Hz, 3H).

Example 305

^{1}H NMR (300 MHz, CD_3OD) δ 7.98-8.05 (m, 1H), 7.86-7.97 (m, 1H), 7.51-7.57 (m, 1H), 7.39-7.50 (m, 3H), 7.25-7.29 (m, 1H), 7.16-7.25 (m, 3H), 6.96-7.06 (m, 1H), 4.68-4.82 (m, 1H), 4.13-4.25 (m, 1H), 3.42-3.59 (m, 2H), 3.30-3.34 (m, 4H), 3.19-3.29 (m, 1H), 2.54 (s, 3H), 2.32-2.51 (m, 3H), 2.16-

2.28 (m, 2H), 1.83-2.10 (m, 8H), 1.66-1.77 (m, 2H), 1.30 (s, 1H), 0.45-0.62 (m, 4H).

Example 306

^{1}H NMR (300 MHz, CD_3OD) δ 7.96-8.04 (m, 1H), 7.86-7.94 (m, 1H), 7.50-7.56 (m, 1H), 7.38-7.48 (m, 3H), 7.16-7.28 (m, 4H), 6.97-7.05 (m, 1H), 4.67-4.82 (m, 1H), 4.13-4.24 (m, 1H), 3.37-3.55 (m, 4H), 3.30-3.34 (m, 4H), 3.18-3.29 (m, 1H), 2.55 (s, 3H), 2.32-2.49 (m, 3H), 2.19-2.28 (m, 1H), 1.85-2.10 (m, 8H), 1.67-1.76 (m, 2H), 1.28-1.32 (m, 1H), 1.02-1.10 (d, J=6.6Hz, 6H).

Example 284

^{1}H NMR (300 MHz, CD_3OD) δ 7.97-8.04 (m, 1H), 7.85-7.97 (m, 1H), 7.50-7.57 (m, 1H), 7.37-7.48 (m, 6H), 7.23-7.30 (m, 1H), 7.14-7.23 (m, 2H), 4.67-4.82 (m, 1H), 4.16-4.27 (m, 1H), 3.63-3.77 (m, 2H), 3.37-3.52 (m, 2H), 3.30-3.34 (m, 3H), 3.18-3.29 (m, 1H), 2.55 (s, 3H), 2.36-2.50 (m, 3H), 2.23-2.34 (m, 1H), 1.83-2.09 (m, 9H), 1.64-1.73 (m, 2H), 1.30 (s, 1H).

Example 285

^{1}H NMR (300 MHz, CD_3OD) δ 7.75-7.94 (m, 3H), 7.50-7.57 (m, 1H), 7.36-7.46 (m, 5H), 7.23-7.30 (m, 1H), 7.14-7.23 (m, 2H), 4.66-4.82 (m, 1H), 4.17-4.28 (m, 1H), 3.62-3.82 (m, 2H), 3.36-3.47 (m, 2H), 3.30-3.34 (m, 4H), 3.11-3.26 (m, 1H), 2.54 (s, 3H), 2.37-2.51 (m, 3H), 2.23-2.34 (m, 1H), 1.85-2.10 (m, 8H), 1.64-1.74 (m, 2H), 1.30 (s, 1H).

Example 365

^{1}H NMR (300 MHz, CD_3OD) δ 7.81-8.10 (m, 2H), 7.47-7.60 (m, 1H), 7.35-7.47 (m, 5H), 7.14-7.31 (m, 3H), 4.69-4.84 (m, 1H), 4.14-4.31 (m, 1H), 3.35-3.49 (m, 2H, under methanol), 3.11-3.27 (m, 1H), 2.50-2.64 (m, 6H), 2.36-2.50 (m, 3H), 2.22-2.36 (m, 1H), 1.82-2.10 (m, 11H), 1.62-1.75 (m, 2H), 1.11-1.20 (d, *J*=6.14 Hz, 2H).

Example 366

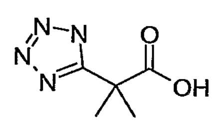
^{1}H NMR (300 MHz, CD_3OD) δ 7.64-7.95 (m, 3H), 7.49-7.59 (m, 1H), 7.34-7.48 (m, 2H), 7.10-7.30 (m, 4H), 6.95-7.06 (m, 1H), 4.72-4.83 (m, 1H), 4.11-4.25 (m, 1H), 3.34-3.53 (m, 5H, under methanol), 3.07-3.29 (m, 1H), 2.76-2.93 (m, 2H), 2.67 (s, 1H), 2.42-2.60 (m, 4H), 2.29-2.42 (m, 1H), 1.74-2.29 (m, 12H), 1.26-1.56 (m, 3H), 0.80-0.96 (m, 3H).

Example 367

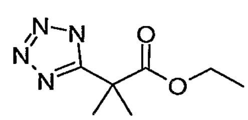
^{1}H NMR (300 MHz, CD_3OD) δ 7.65-7.92 (m, 2H), 7.47-7.65 (m, 2H), 7.37-7.47 (m, 1H), 7.12-7.36 (m, 5H), 7.04-7.12 (m, 1H), 4.69-4.83 (m, 1H), 4.08-4.31 (m, 1H), 3.34-3.47 (m, 3H, under methanol), 3.13-3.28 (m, 3H), 2.32-2.64 (m, 8H), 2.20-2.32 (m, 1H), 1.79-2.13 (m, 9H), 1.64-1.78 (m, 2H), 1.24-1.43 (m, 5H).

Synthesis of Acids

Acid 1: *2-methyl-2-(1H-tetraazol-5-yl)propanoic acid*

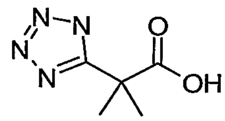


Ethyl 2-methyl-2-(1H-tetraazol-5-yl)propanoate



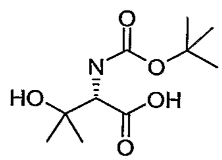
The title compound was prepared from ethyl 2-cyano-2-methylpropanoate (3.67 g, 26 mmoles) via the literature procedure [*J. Org. Chem.*, 58(15), 4139 (1993)] to give 3.83 g (80%) of pure product as an amber solid. ^{13}C NMR (300 MHz, $CDCl_3$) δ 174.04, 159.73, 62.74, 42.30, 25.74, 14.12.

2-methyl-2-(1H-tetraazol-5-yl)propanoic acid



Ethyl 2-methyl-2-(1*H*-tetraazol-5-yl) propanoate (1.50 g, 8.14 mmoles) was dissolved in 8 mL EtOH and treated with 6.7 mL 6N NaOH at ambient temperature for 18h. The reaction mixture was concentrated to dryness and the resultant solid was extracted with EtOH. Inorganics were filtered off and the filtrate were concentrated to give the title compound (1.24 g, 7.94 mmoles, 98%) as a tan solid. ^{13}C NMR (300 MHz, D_2O) δ 176.88, 159.60, 41.69, 24.07.

Acid 2: *N-(tert-butoxycarbonyl)-3-hydroxy-L-valine*

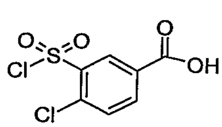


3-Hydroxy-L-valine (500 mg, 3.75 mmoles) in 10 mL DMF with TEA (1 eq.) was treated with di(*tert*-butyl)dicarbonate (3.75 mmoles, 1 eq.) for 18h at ambient temperature. The reaction mixture was diluted with water, pH adjusted to 10 with 6 N NaOH, washed with EtOAc, and the aqueous phase was isolated. The aqueous phase was combined with fresh DCM, pH adjusted to 4 with 1N HCl. The organic phase was isolated, dried over $MgSO_4$, filtered and concentrated to give the title compound (68%) as a clear oil. ^1H NMR (300 MHz, CD_3OD) δ 4.09 (s, 1H), 1.46 (s, 9H), 1.30 (s, 3H), 1.26 (s, 3H).

<u>Synthesis of Sulfonamide Benzoid Acids via Chlorosulfonylation/amination Procedure</u>

<u>Method G – primary sulfonamide, lower sulfonamides</u>

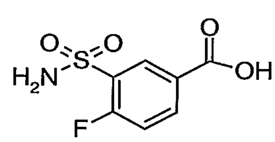
4-chloro-3-(chlorosulfonyl)benzoic acid



At 5-10 °C, to stirred chlorosulfonic acid (200 mL) was added 4-chlorobenzoic acid (78 g, 0.5 mol). The reaction mixture was then brought up to 150~160 °C for 5 hours. After being cooled down to room temperature, the reaction mixture was slowly poured onto a large amount of ice and extracted with ether. The combined organic extracts were washed with ice water and dried over anhydrous magnesium sulfate. Evaporation of solvents afforded 4-chloro-3-(chlorosulfonyl)benzoic acid as a solid (76 g), which was directly used in the next steps.

4-Fluoro-3-(chlorosulfonyl)benzoic acid, 2,6-difluoro-3-(chlorosulfonyl)benzoic acid, 2,6-dichloro-3-(chlorosulfonyl)benzoic acid, 3,4-difluoro-5-(chloro-sulfonyl)benzoic acid, 2,6-methyl-3-(chlorosulfonyl) benzoic acid, 4-bromo-3-(chlorosulfonyl)benzoic acid, 2,6-difluoro-3-(chlorosulfonyl)benzoic acid, 4-methoxy-3-(chlorosulfonyl)benzoic acid, 5-chloro-3-(chloro-sulfonyl)-2-hydroxybenzoic acid, 2-chloro-5-(chloro-sulfonyl)benzoic acid, and 3-(chlorosulfonyl)-4-fluorobenzoic acid were prepared with the same procedure as above except for varying temperatures and heating time based on substrates. In some cases, the pure product was obtained as a precipitate from the ice quench in which case the product was filtered off and no extraction was necessary.

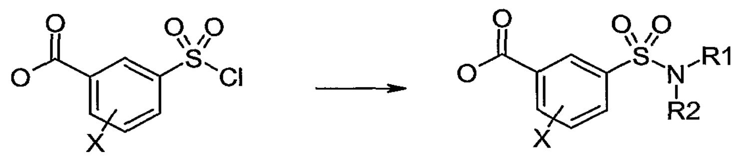
Synthesis of 3-(aminosulfonyl)-4-fluorobenzoic acid



To ~50 mL of liquid ammonia at -78 °C was added 7.0 grams of freshly prepared 4-fluoro-3-(chloro-sulfonyl)benzoic acid. The excess ammonia was then naturally evaporated to dryness overnight at room temperature. The crude solid was dissolved in water (50 mL) and acidified to pH~6 with HCl (conc.). After removal of the precipitate by filtration, the filtrate was further acidified to pH ~1. The desired product was precipitated and collected by filtration (5.0 g). ES LC-MS m/z (M-1)- 218.

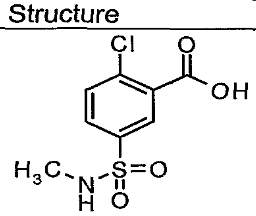
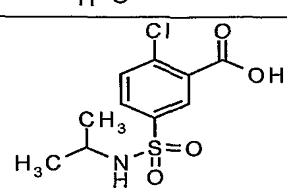
Acids **16, 22**, **31**, **37**, **43**, and **49** were prepared by this same method. Yields and representative data are included in the accompanying tables.

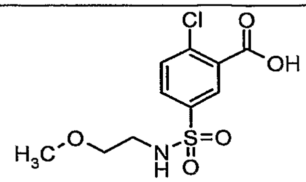
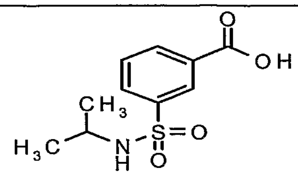
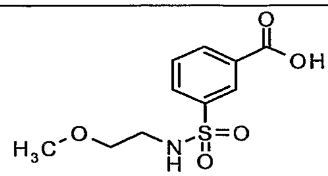
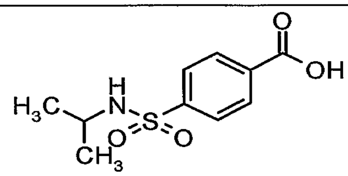
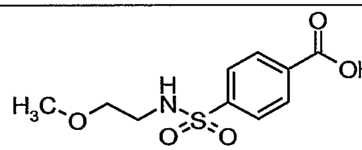
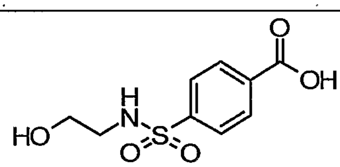
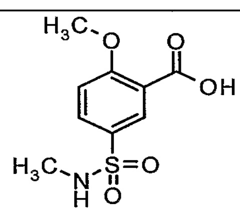
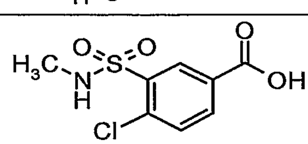
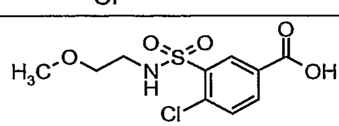
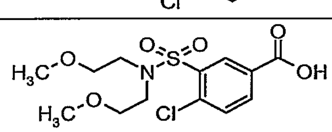
Method H – secondary and tertiary sulfonamides

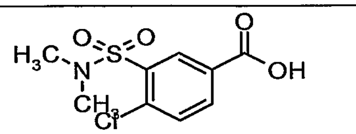
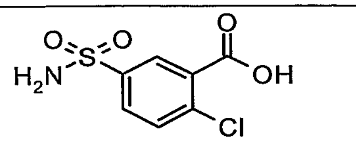
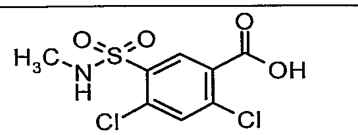
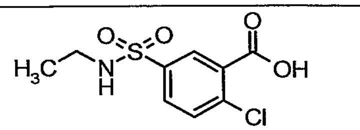
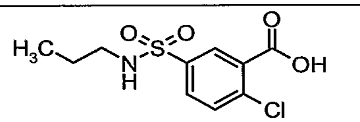
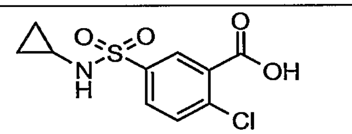
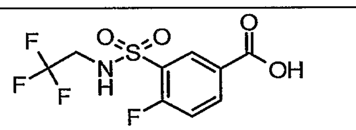
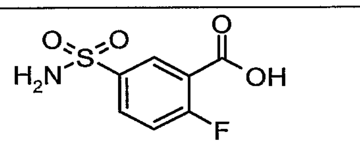
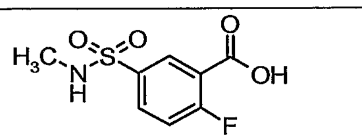
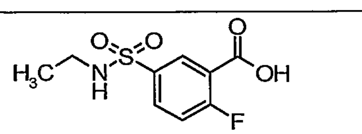
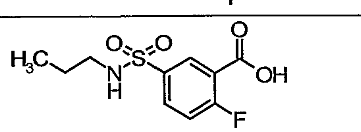
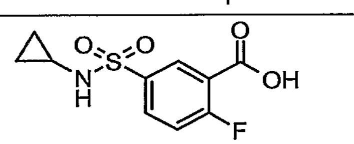


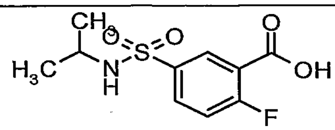
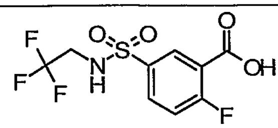
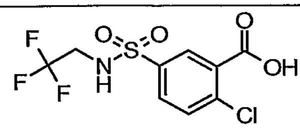
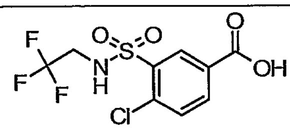
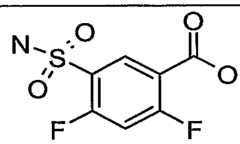
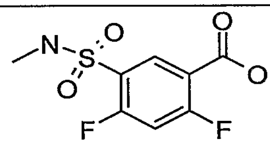
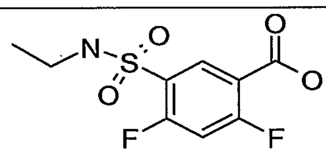
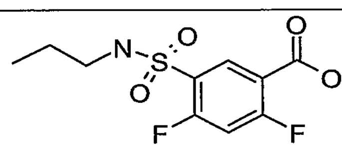
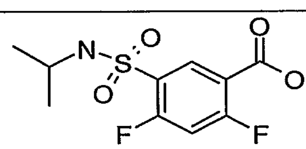
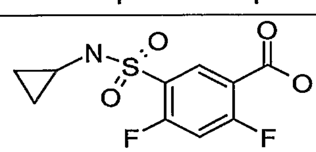
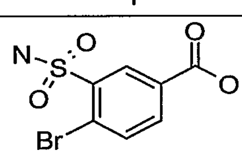
To the sulfonyl halide (8.00 mmoles) in 6 mL THF was added a 2N solution of the amine (24.0 mmoles, 3 eq.) in THF and the mixture was stirred overnight at ambient temperature. The reaction mixture was concentrated to dryness and partitioned between DCM and H_2O. The pH was adjusted to 10 with 6N NaOH and the aqueous phase was isolated. The aqueous phase was acidified to pH 2 with 6N HCl and the reaction mixture was stirred vigorously to give a white precipitate. The precipitate was filtered off, washed with water and air dried to give the desired product. In cases where precipitation did not occur, the aqueous phase was extracted with EtOAc, organic phases were combined, dried over $MgSO_4$, filtered, and concentrated to give the desired products. Yields and representative data are included in the accompanying tables.

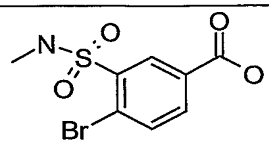
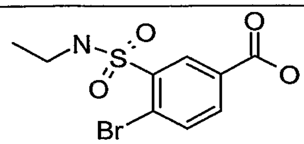
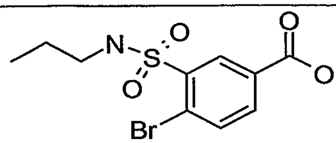
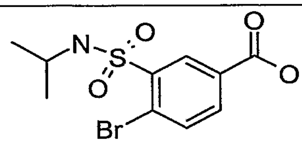
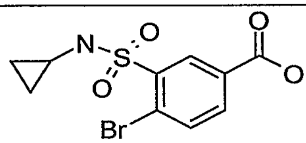
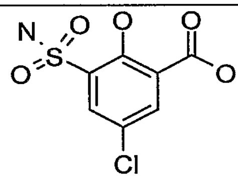
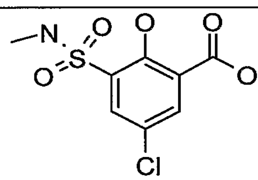
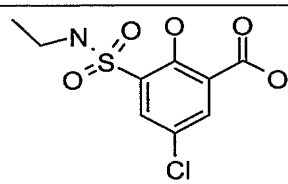
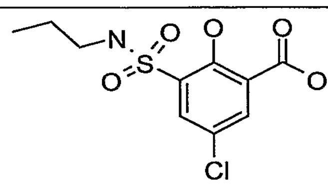
Table of Carboxylic Acids

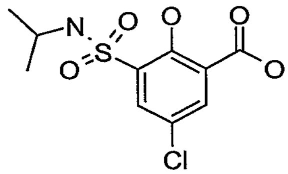
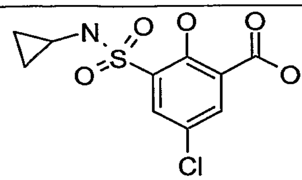
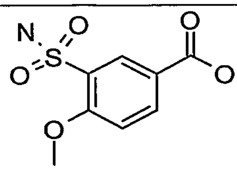
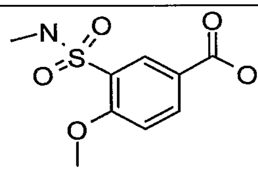
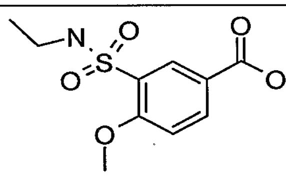
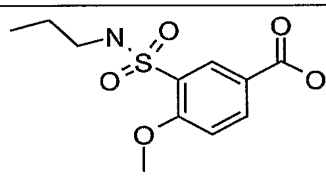
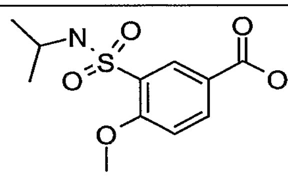
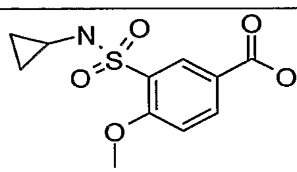
Acid #	Structure	Yield	ES-LCMS	Ion	Method
Acid 3		10	248.20	(M+H)	H
Acid 4		69	276.26	(M-1)	H

Acid 5		68	292.21	(M-1)	H
Acid 6		84	242.29	(M-1)	H
Acid 7		53	258.27	(M-1)	H
Acid 8		86	242.30	(M-1)	H
Acid 9		66	258.27	(M-1)	H
Acid 10		74	244.26	(M-1)	H
Acid 11		70	244.22	(M-1)	H
Acid 12		46	249.85, 251.83	(M+H)	H
Acid 13		10	294.10, 296.10	(M+H)	H
Acid 14		10	352.12, 354.12	(M+H)	H

Acid 15		20	264.14	(M+H)	H
Acid 16		70	233.88	(M-1)	G
Acid 17		62	282.19	(M-1)	H
Acid 18		69	263.87, 265.92	(M+H)	H
Acid 19		75	277.93, 279.88	(M+H)	H
Acid 20		79	275.96, 277.85	(M+H)	H
Acid 21		36	300.08	(M-1)	H
Acid 22		62	217.92	(M-1)	G
Acid 23		31	232.05	(M-1)	H
Acid 24		36	245.98	(M-1)	H
Acid 25		80	260.00	(M-1)	H
Acid 26		83	258.03	(M-1)	H

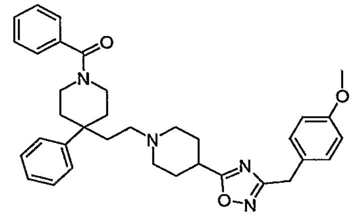
Acid 27		62	260.02	(M-1)	H
Acid 28		55	300.07	(M-1)	H
Acid 29		47	316.03	(M-1)	H
Acid 30		34	316.01	(M-1)	H
Acid 31		48	236	(M-1)	G
Acid 32		54	250	(M-1)	H
Acid 33		58	264	(M-1)	H
Acid 34		61	278	(M-1)	H
Acid 35		66	278	(M-1)	H
Acid 36		56	276	(M-1)	H
Acid 37		39	279	(M-1)	G

Acid 38		41	293	(M-1)	H
Acid 39		33	307	(M-1)	H
Acid 40		42	321	(M-1)	H
Acid 41		38	321	(M-1)	H
Acid 42		29	319	(M-1)	H
Acid 43		61	250	(M-1)	G
Acid 44		68	264	(M-1)	H
Acid 45		62	278	(M-1)	H
Acid 46		57	292	(M-1)	H

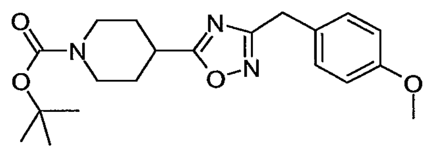
Acid 47		65	292	(M-1)	H
Acid 48		70	290	(M-1)	H
Acid 49		49	230	(M-1)	G
Acid 50		47	244	(M-1)	H
Acid 51		53	258	(M-1)	H
Acid 52		42	272	(M-1)	H
Acid 53		51	272	(M-1)	H
Acid 54		44	270	(M-1)	H

Example 368

1-benzoyl-4-(2-{4-[3-(4-methoxybenzyl)-1,2,4-oxadiazol-5-yl]piperidin-1-yl}ethyl)-4-phenylpiperidine

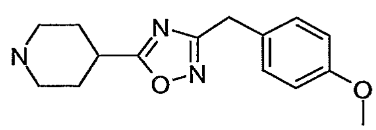


tert-butyl 4-[3-(4-methoxybenzyl)-1,2,4-oxadiazol-5-yl]piperidine-1-carboxylate



1-(*tert*-Butoxycarbonyl)piperidine-4-carboxylic acid (2.29 g, 10.0 mmoles) in 10 mL DMF was treated with 1,1'-carbonyldiimidazole (1.62 g, 10 mmoles, 1 eq.) at ambient temperature for 30 min until CO_2 evolution ceased. (1*Z*)-*N*'-hydroxy-2-(4-methoxyphenyl)ethanimidamide [*J. Med. Chem.*, 36(11), 1529 (1993)] (10.0 mmoles, 1 eq.) was dissolved in 5 mL DMF and added to the reaction mixture. The reaction mixture was heated at 70 °C for 6h then at 120°C for an additional 6h. The reaction mixture was diluted with EtOAc and washed successively with water, 1N citric acid, saturated aqueous $NaHCO_3$, and brine. The organic phase was isolated, dried over $MgSO_4$, filtered and concentrated to give the title compound as an amber oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26 (d, 2H, J=8.5Hz), 6.88 (d, 2H, J=8.5Hz), 4.10 (m, 2H), 4.00 (s, 2H), 3.80 (s, 3H), 3.08 (m, 1H), 2.97-2.90 (m, 2H), 2.04 (m, 2H), 1.87-1.73 (m, 2H), 1.47 (s, 9H). ES-LCMS *m/z* 395.99 (M+Na).

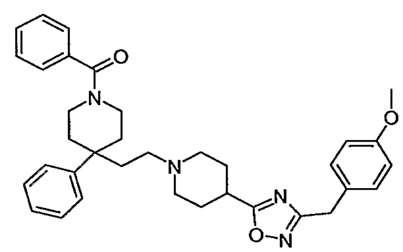
4-[3-(4-methoxybenzyl)-1,2,4-oxadiazol-5-yl]piperidine



Tert-butyl 4-[3-(4-methoxybenzyl)-1,2,4-oxadiazol-5-yl]piperidine-1-carboxylate was treated with 10 mL TFA/DCM (1:1) for 30 min at ambient

temperature. The reaction mixture was concentrated and the crude product was crystalized from EtOAc/Et_2O, filtered and dried to give the TFA salt of 4-[3-(4-methoxybenzyl)-1,2,4-oxadiazol-5-yl]piperidine as a tan solid (1.23g, 3.17mmol, 32%, 3 steps). ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.22 (d, 2H, J=8.5Hz), 6.88 (d, 2H, J=8.5Hz), 4.00 (s, 2H), 3.72 (s, 3H), 3.43-3.29 (m, 2H), 3.02 (m, 2H), 2.17 (m, 2H), 1.92-1.80 (m, 2H). ES-LCMS *m/z* 274.30 (M+H).

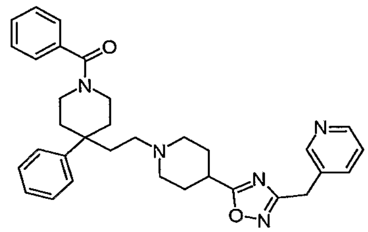
1-benzoyl-4-(2-{4-[3-(4-methoxybenzyl)-1,2,4-oxadiazol-5-yl]piperidin-1-yl}ethyl)-4-phenylpiperidine



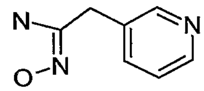
The TFA salt of 4-[3-(4-methoxybenzyl)-1,2,4-oxadiazol-5-yl]piperidine (29 mg, 0.076 mmol) was combined with (1-benzoyl-4-phenylpiperidin-4-yl)acetaldehyde (21 mg, 0.069 mmol) in 2 mL DCM and treated with $NaBH(OAc)_3$ (43 mg, 0.203 mmol) at ambient temperature with agitation for 18h. 1 mL of saturated aqueous $NaHCO_3$ was added and agitated 1h. The organic phase was separated and concentrated. The crude product was purified by HPLC to give 1-benzoyl-4-(2-{4-[3-(4-methoxybenzyl)-1,2,4-oxadiazol-5-yl]piperidin-1-yl}ethyl)-4-phenylpiperidine (16.1 mg, 0.026 mmol, 38%) as the formate salt. ^{1}H NMR (300 MHz, CD_3OD) δ 7.49-7.37 (m, 9H), 7.28 (m, 1H), 7.20 (d, 2H, J=8.8Hz), 6.86 (d, 2H, J=8.8Hz), 4.19 (m, 1H), 3.96 (s, 2H), 3.76 (s, 3H), 3.59 (m, 1H), 3.37-3.20 (m, 3H), 3.12-2.95 (m, 3H), 2.45-1.73 (m, 13H). ES-LCMS *m/z* 565.29 (M+H). HRMS $C_{35}H_{40}N_4O_3$ *m/z* 565.3179 $(M+H)_{Cal.}$ 565.3183 $(M+H)_{Obs.}$.

Example 369

3-[(5-{1-[2-(1-benzoyl-4-phenylpiperidin-4-yl)ethyl] piperidin-4-yl}-1,2,4-oxadiazol-3-yl)methyl]pyridine

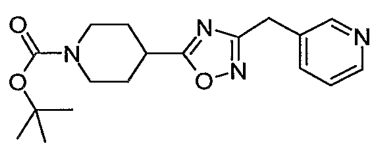


(1Z)-N'-hydroxy-2-pyridin-3-ylethanimidamide



Hydroxylamine hydrochloride (0.87 g, 0.0125 mmol) was added to 0.5M $NaOCH_3$ (25 mL, 0.0125 mmol) and stirred at ambient temperature for 30 min. The reaction mixture was filtered and the filtrate was combined with pyridin-3-ylacetonitrile (1.18 g, 0.010 mmol). The resultant mixture was heated at reflux for 2h, stirred at ambient temperature overnight and concentrated to give crude (1*Z*)-*N*'-hydroxy-2-pyridin-3-ylethanimidamide which was used immediately without purification. ES-LCMS *m/z* 152.18 (M+H).

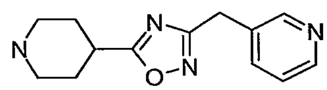
tert-butyl 4-[3-(pyridin-3-ylmethyl)-1,2,4-oxadiazol-5-yl]piperidine-1-carboxylate



1-(*Tert*-butoxycarbonyl)piperidine-4-carboxylic acid (2.29 g, 0.010 mmol) was treated with 1,1'-carbonyldiimidazole (1.62 g, 0.010 mmol) in DMF (5 mL) at ambient temperature for 30 min. Following this activation period, the crude (1*Z*)-*N*'-hydroxy-2-pyridin-3-ylethanimidamide (0.010 mmol) was added and the reaction mixture heated at 70 °C for 6h followed by 120°C for an additional 6h. The reaction mixture was cooled and partitioned between

EtOAc and water. The organic phase was separated, washed successively with saturated $NaHCO_3$ and brine, dried over $MgSO_4$, filtered and concentrated to give *tert*-butyl 4-[3-(pyridin-3-ylmethyl)-1,2,4-oxadiazol-5-yl]piperidine-1-carboxylate. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.61 (s, 1H), 8.53 (m, 1H), 7.67 (d, 1H, J=7.7Hz), 7.28 (m, 1H), 4.20-4.05 (m, 2H), 4.08 (s, 2H), 3.08 (m, 1H), 2.94 (m, 2H), 2.04 (m, 2H), 1.87-1.73 (m, 2H), 1.47 (s, 9H). ES-LCMS *m/z* 367.36 (M+Na).

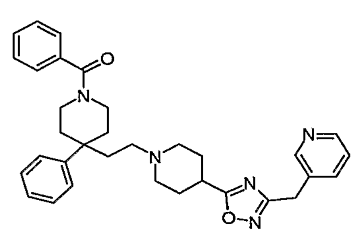
3-[(5-piperidin-4-yl-1,2,4-oxadiazol-3-yl)methyl] pyridine



tert-Butyl 4-[3-(pyridin-3-ylmethyl)-1,2,4-oxadiazol-5-yl]piperidine-1-carboxylate was treated with 10 mL TFA/DCM (1:1) for 30 min at ambient temperature. The reaction mixture was concentrated to give the di-TFA salt of 3-[(5-piperidin-4-yl-1,2,4-oxadiazol-3-yl)methyl]pyridine as an amber oil (4.0 g, 8.47 mmol, 85%, 3 steps). ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.78 (s, 1H), 8.70 (d, 1H, J=5.0Hz), 8.51 (br.s, 1H), 8.18 (d, 1H, J=7.9Hz), 7.75 (m, 1H), 4.30 (s, 2H), 3.44-3.30 (m, 3H), 3.09-3.00 (m, 2H), 2.20-2.16 (m, 2H), 1.93-1.80 (m, 2H).

Example 370

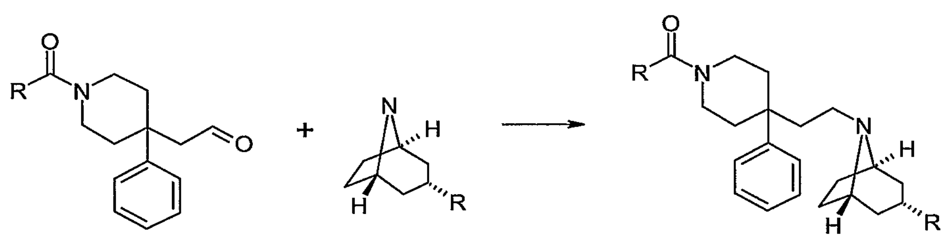
3-[(5-{1-[2-(1-benzoyl-4-phenylpiperidin-4-yl)ethyl] piperidin-4-yl}-1,2,4-oxadiazol-3-yl)methyl]pyridine



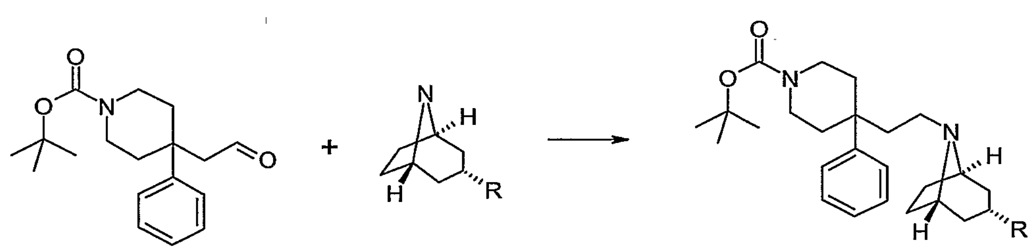
The TFA salt of 3-[(5-piperidin-4-yl-1,2,4-oxadiazol-3-yl)methyl]pyridine (27 mg, 0.076 mmol) was combined with (1-benzoyl-4-phenylpiperidin-4-yl)acetaldehyde (21 mg, 0.069 mmol) in 2 mL DCM and treated with $NaBH(OAc)_3$ (43 mg, 0.203 mmol) at ambient temperature with agitation for

18h. 1mL of saturated aqueous $NaHCO_3$ was added and agitated 1h. The organic phase was separated and concentrated. The crude product was purified by HPLC (METHOD) to give 3-[(5-{1-[2-(1-benzoyl-4-phenylpiperidin-4-yl)ethyl]piperidin-4-yl}-1,2,4-oxadiazol-3-yl)methyl]pyridine (14.2 mg, 0.024 mmol, 34%) as the formate salt. ^1H NMR (300 MHz, CD_3OD) δ 8.52-8.44 (m, 2H), 7.80 (d, 1H, J=7.9Hz), 7.48-7.38 (m, 10H), 7.26 (m, 1H), 4.19 (m, 1H), 4.13 (s, 2H), 3.59 (m, 1H), 3.36-3.29 (m, 3H), 3.12-3.02 (m, 3H), 2.47-1.45 (m, 13H). ES-LCMS *m/z* 536.25 (M+H). HRMS $C_{33}H_{37}N_5O_2$ *m/z* 536.3026 $(M+H)_{Cal.}$ 536.3018 $(M+H)_{Obs.}$.

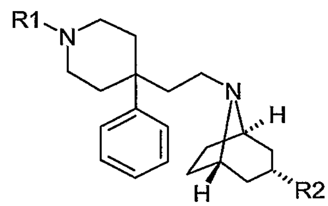
Reductive Amination Method I

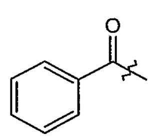
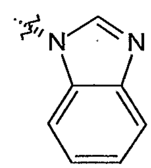
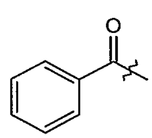
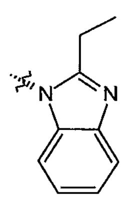
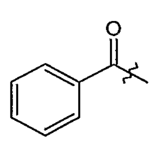
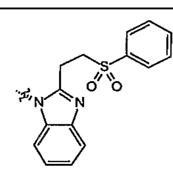
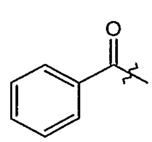
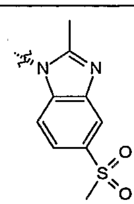


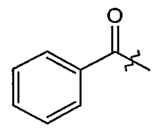
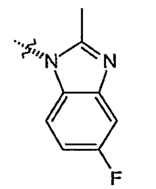
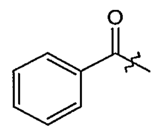
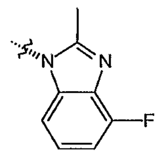
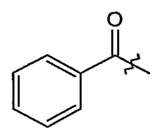
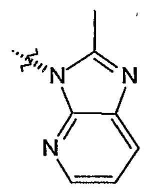
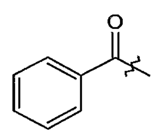
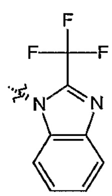
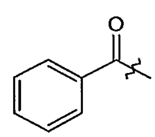
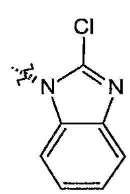
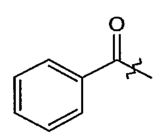
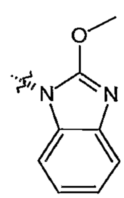
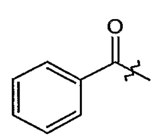
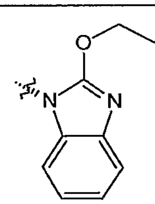
The TFA or HCl salt of the amine (390 µmoles) was combined with (1-benzoyl-4-phenylpiperidin-4-yl)acetaldehyde (120 mg, 390 µmoles, 1 eq.) in 4mL DCE and/or 4mL DMF and treated with $NaBH(OAc)_3$ (585 µmoles, 1.5 eq.) with or without TEA (780 µmoles, 2 eq.) at ambient temperature with agitation for 18h. The reaction mixture was concentrated, dissolved in 5 mL DCM, and agitated 1h with 5 mL of saturated aqueous $NaHCO_3$. The organic phase was separated and concentrated. The crude product was purified either by normal phase flash chromatography (SiO_2, $CHCl_3/CH_3OH$) or by reverse phase mass-directed HPLC as described in Preparative HPLC Conditions A. Yields and representative data are included in the accompanying tables.

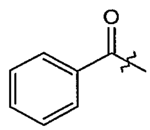
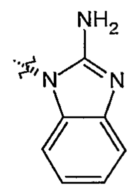
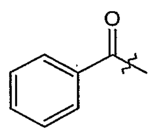
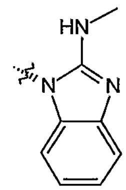
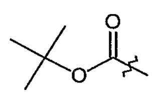
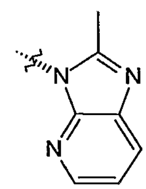


The HCl salt of the amine (1.66 mmoles) was combined with *tert*-butyl 4-(2-oxoethyl)-4-phenyl piperidine-1-carboxylate (1.66 mmoles, 1 eq.) in 10 mL DCE and 10 mL DCM and treated with $NaBH(OAc)_3$ (2.49 mmoles, 1.5 eq.) with TEA (3.33 moles, 2 eq.) at ambient temperature with agitation for 18h. The reaction mixture was washed with saturated aqueous $NaHCO_3$, the organic phase separated, dried over $MgSO_4$, filtered and concentrated. The crude product was purified by normal phase flash chromatography (SiO_2, $CHCl_3/CH_3OH$) to give the desired product. Yields and representative data are included in the accompanying tables.



Example #	Amine #	R1	R2	% yield	LCMS result	Ion	Method
371	Amine 1			55	519.32	(M+H)	I
372	Amine 2			17	547.35	(M+H)	I
373	Amine 3			26	687.30	(M+H)	I
374	Amine 4			64	611.26	(M+H)	I

375	Amine 5			53	551.18	(M+H)	I
376	Amine 6			50	551.18	(M+H)	I
377	Amine 7			52	534.19	(M+H)	I
378	Amine 8			57	587.14	(M+H)	I
379	Amine 9			7	553.12	(M+H)	I
380	Amine 10			37	549.38	(M+H)	I
381	Amine 11			22	563.40	(M+H)	I

382	Amine 12			11	534.43	(M+H)	I
383	Amine 13			42	548.36	(M+H)	I
384	Amine 14			68	530.21	(M+H)	J

Additional analytical data of selected compounds from table above:

Example 371

Endo-1-{8-[2-(1-benzoyl-4-phenylpiperidin-4-yl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1*H*-benzimidazole

^{1}H NMR (300 MHz, CD_3OD) δ 8.46 (s, 1H), 7.70 (m, 1H), 7.51-7.28 (m, 13H), 4.80 (m, 1H), 4.23 (m, 1H), 3.71 (m, 2H), 3.62 (m, 1H), 3.35-3.22 (m, 2H), 2.74-1.67 (m, 16H). HRMS $C_{34}H_{38}N_4O$ *m/z* 519.3124 $(M+H)_{Cal.}$; 519.3110 $(M+H)_{Obs.}$.

Example 372

Endo-1-{8-[2-(1-benzoyl-4-phenylpiperidin-4-yl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-2-ethyl-1*H*-benzimidazole

^{1}H NMR (300 MHz, CD_3OD) δ ppm 1.35 (t, *J*=7.8 Hz, 3H), 1.76-2.53 (m, 16H), 2.89 (q, *J*=7.7Hz, 2H), 3.31-3.46 (m, 4H), 3.62 (m, 1H), 4.19 (m, 1H), 4.80 (m, 1H), 7.17-7.29 (m, 3H), 7.39-7.49 (m, 10H), 7.57 (m, 1H).

Example 380

Endo-1-{8-[2-(1-benzoyl-4-phenylpiperidin-4-yl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-2-methoxy-1*H*-benzimidazole

^{1}H NMR (300 MHz, CD_3OD) δ 7.49-7.39 (m, 10H), 7.32 (m, 1H), 7.24 (m, 1H), 7.16 (m, 2H), 4.81 (pent, 1H), 4.25 (m, 1H), 4.17 (s, 3H), 3.75 (m, 2H), 3.63 (m, 1H), 3.35-3.27 (m, 2H), 2.65-1.79 (m, 16H). ES-LCMS *m/z* 549.38 (M+H). HRMS $C_{35}H_{40}N_4O_2$ *m/z* 549.3230 $(M+H)_{Cal.}$; 549.3217 $(M+H)_{Obs.}$.

Example 381

Endo-1-{8-[2-(1-benzoyl-4-phenylpiperidin-4-yl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-2-ethoxy-1*H*-benzimidazole

^{1}H NMR (300 MHz, CD_3OD) δ 7.51-7.39 (m, 10H), 7.32 (m, 1H), 7.24 (m, 1H), 7.16 (m, 2H), 4.85 (pent, 1H), 4.57 (q, 2H, J = 7.0Hz), 4.23 (m, 1H), 3.73 (m, 2H), 3.63 (m, 1H), 3.35-3.27 (m, 2H), 2.65-1.79 (m, 16H). ES-LCMS *m/z* 563.40 (M+H). HRMS $C_{36}H_{42}N_4O_2$ *m/z* 563.3386 $(M+H)_{Cal.}$; 563.3368 $(M+H)_{Obs.}$.

Example 382

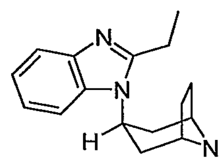
Endo-1-{8-[2-(1-benzoyl-4-phenylpiperidin-4-yl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1*H*-benzimidazol-2-amine

^{1}H NMR (300 MHz, CD_3OD) δ 7.48-7.40 (m, 9H), 7.28 (m, 3H), 7.13 (m, 2H), 4.61 (pent, 1H), 4.19 (m, 1H), 3.59 (m, 1H), 3.39-3.27 (m, 4H), 2.48-1.65 (m, 16H). HRMS $C_{34}H_{39}N_5O$ *m/z* 534.3233 $(M+H)_{Cal.}$; 534.3241 $(M+H)_{Obs.}$.

Preparation of Amines 1-14:

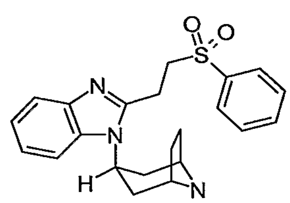
Amine 1: prepared by the literature procedure described in WO 00/38680.

Amine 2: *Endo-1-(8-azabicyclo[3.2.1]oct-3-yl)-2-ethyl-1H-benzimidazole*



Endo-tert-butyl 3-[(2-aminophenyl)amino]-8-azabicyclo[3.2.1]octane-8-carboxylate (WO 00/38680) (2.5 g, 7.80 mmol) was treated with 20 mL 1,1,1-triethoxypropane at reflux for 3h. The reaction mixture was concentrated to dryness, redissolved in CH_3OH (10 mL), and treated with 6 N HCl at reflux for 1h. The reaction mixture was concentrated to dryness, chased with EtOH, and triturated with EtOH to give a solid that was filtered and dried to give the HCl salt of *endo*-1-(8-azabicyclo[3.2.1]oct-3-yl)-2-ethyl-1*H*-benzimidazole (1.35 g, 4.11 mmol, 53%) as a grey solid. ^{1}H NMR (300 MHz, D_2O) δ 7.72-7.65 (m, 2H), 7.49-7.46 (m, 2H), 4.99 (m, 1H) 4.19 (m, 2H), 3.10 (q, 2H, *J*=7.6Hz), 2.76-2.70 (m, 2H), 2.40-2.18 (m, 6H), 1.35 (t, 3H, *J*=7.6Hz). ES-LCMS *m/z* 256.07 (M+H).

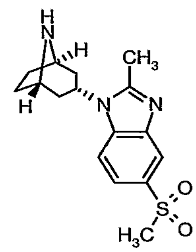
Amine 3: *Endo-1-(8-azabicyclo[3.2.1]oct-3-yl)-2-[2-(phenylsulfonyl)ethyl]-1H-benzimidazole*



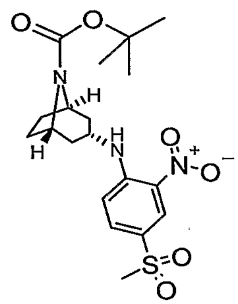
Endo-tert-butyl 3-[(2-aminophenyl)amino]-8-azabicyclo[3.2.1]octane-8-carboxylate (WO 00/38680) (1.8 g, 5.70 mmol) was treated with 20 mL [(3,3,3-triethoxypropyl)sulfonyl]benzene at 150 °C for 3h. The reaction mixture was concentrated to dryness, redissolved in CH_3OH (10 mL), and treated with 6 N HCl at reflux for 1h. The reaction mixture was concentrated to dryness, chased with EtOH, and triturated with EtOH to give a solid that was filtered and dried to give the di-HCl salt of *endo*-1-(8-azabicyclo[3.2.1]oct-3-yl)-2-[2-(phenylsulfonyl)ethyl]-1*H*-benzimidazole (1.68 g, 3.59 mmol, 63%) as a grey solid. ^{1}H NMR (300 MHz, D_2O) δ 7.72-7.69 (m, 2H), 7.64 (m, 1H), 7.58 (m, 1H), 7.49-7.44 (m, 3H), 7.36 (m, 2H), 4.99 (m, 1H) 4.19 (m, 2H), 3.93

(t, 2H, *J*=7.0Hz), 3.63 (t, 2H, *J*=7.0Hz), 2.75-2.65 (m, 2H), 2.33-2.15 (m, 6H). ES-LCMS *m/z* 396.14 (M+H).

Amine 4: *Endo-1-[(1R,5S)-8-azabicyclo[3.2.1]oct-3-yl]-2-methyl-5-(methylsulfonyl)-1H-benzimidazole*

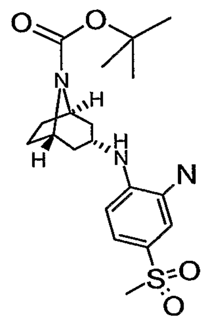


Endo-tert-butyl (1R,5S)-3-{[4-(methylsulfonyl)-2-nitrophenyl]amino}-8-azabicyclo[3.2.1]octane-8-carboxylate



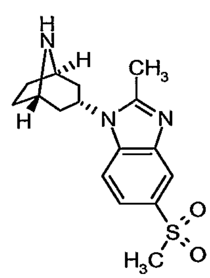
Endo-tert-butyl (1*R*,5*S*)-3-amino-8-azabicyclo[3.2.1]octane-8-carboxylate (WO 00/38680) (1.5 g, 6.66 mmoles) was treated with 1-fluoro-4-(methylsulfonyl)-2-nitrobenzene (1.46 g, 1 eq.) in 10 mL NMP with DIPEA (947 mg, 1.1 eq.) at 70°C for 3h. The reaction mixture was diluted with 5 mL NMP, cooled to ambient temperature, and water added to incipient cloudiness. The reaction mixture was stirred until a heavy precipitate formed. The precipitate was filtered off, washed successively with NMP/water (1:1) and water, and air dried to give *endo-tert*-butyl (1*R*,5*S*)-3-{[4-(methylsulfonyl)-2-nitrophenyl]amino}-8-azabicyclo [3.2.1]octane-8-carboxylate (2.21 g, 78%) as a yellow solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.90 (d, 1H, *J*=7.0Hz), 8.53 (d, 1H, *J*=2.0Hz), 7.94 (dd, 1H, *J*=9.2, 2.0Hz), 7.17 (d, 1H, *J*=9.3Hz), 4.11 (m, 3H), 3.21 (s, 3H), 2.16 (m, 2H), 1.94 (m, 4H), 1.80 (m, 2H), 1.42 (s, 9H).

Endo-tert-butyl (1R,5S)-3-{[2-amino-4-(methylsulfonyl) phenyl]amino}-8-azabicyclo[3.2.1]octane-8-carboxylate



Endo-tert-butyl (1*R*,5*S*)-3-{[4-(methyl sulfonyl)-2-nitrophenyl]amino}-8-azabicyclo[3.2.1] octane-8-carboxylate (2.21 g, 5.19 mmoles) was subjected to catalytic hydrogenation with 10% Pd/C (260 mg) in EtOH/EtOAc (1:1, 100 mL) under 1atm H_2(g) for 16h. The catalyst was filtered off and the filtrate concentrated to a purple oil which was carried on to the next step without further characterization.

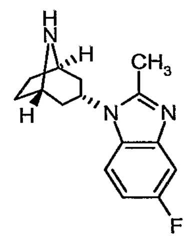
Endo-1-[(1R,5S)-8-azabicyclo[3.2.1]oct-3-yl]-2-methyl-5-(methylsulfonyl)-1H-benzimidazole



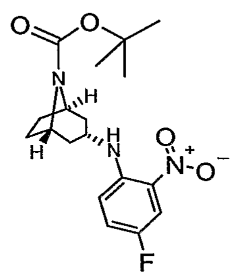
Endo-tert-butyl (1*R*,5*S*)-3-{[2-amino-4-(methylsulfonyl)phenyl]amino}-8-azabicyclo[3.2.1] octane-8-carboxylate was treated with 1,1,1-triethoxyethane at reflux for 2h. The reaction mixture was concentrated to dryness, redissolved in CH_3OH (10 mL), and treated with 6 N HCl at reflux for 1h. The reaction mixture was concentrated to dryness, chased with EtOH, and triturated with EtOH to give a solid that was filtered and dried to give the di-HCl salt of *endo-tert*-butyl (1*R*,5*S*)-3-{[2-amino-4-(methylsulfonyl) phenyl]amino}-8-azabicyclo[3.2.1]octane-8-carboxylate as a grey solid. ^{1}H

NMR (300 MHz, D_2O) δ 8.27 (m, 1H), 7.98-7.89 (m, 2H), 5.00 (m, 1H), 4.20 (m, 2H), 3.21 (s, 3H), 2.77 (s, 3H), 2.79-2.70 (m, 2H), 2.35-2.15 (6H).

Amine 5: *Endo-1-[(1R,5S)-8-azabicyclo[3.2.1]oct-3-yl]-5-fluoro-2-methyl-1H-benzimidazole*

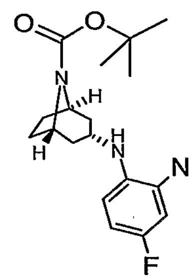


Endo-tert-butyl (1R,5S)-3-[(4-fluoro-2-nitrophenyl) amino]-8-azabicyclo[3.2.1]octane-8-carboxylate



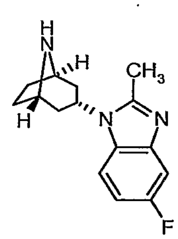
Endo-tert-butyl (1*R*,5*S*)-3-amino-8-azabicyclo[3.2.1]octane-8-carboxylate (WO 00/38680) (2.0 g, 8.88 mmoles) was treated with 1,4-difluoro-2-nitrobenzene (1.41 g, 1 eq.) in 10 mL NMP with DIPEA (1.26 g, 1.1 eq.) at 70 °C for 16h. The reaction mixture was cooled to ambient temperature, and water (4 mL) added to incipient cloudiness. The reaction mixture was stirred until a heavy precipitate formed. The precipitate was filtered off, washed successively with NMP/water (1:1) and water, and air dried to give *tert*-butyl (1*R*,5*S*)-3-[(4-fluoro-2-nitrophenyl)amino]-8-azabicyclo[3.2.1]octane-8-carboxylate as an orange solid (2.74g , 7.50 mmoles, 84%). ^1H NMR (300 MHz, $CDCl_3$) δ 8.66 (d, 1H, *J*=5.7Hz), 7.93 (m, 1H), 7.27 (m, 1H), 6.72 (m, 1H), 4.29 (m, 3H), 3.91 (m, 1H), 2.40-2.29 (m, 2H), 2.15-2.01 (m, 4H), 1.80 (m, 2H), 1.50 (s, 9H).

Endo-tert-butyl (1R,5S)-3-[(2-amino-4-fluorophenyl) amino]-8-azabicyclo[3.2.1]octane-8-carboxylate



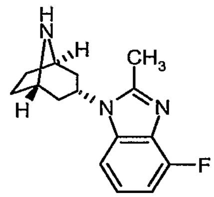
Endo-tert-butyl (1*R*,5*S*)-3-[(4-fluoro-2-nitrophenyl)amino]-8-azabicyclo[3.2.1]octane-8-carboxylate (2.74 g, 7.50 mmoles) was subjected to catalytic hydrogenation with 10% Pd/C (300 mg) in EtOH/EtOAc (1:1, 80 mL) under 1atm H_2(g) for 16h. The catalyst was filtered off and the filtrate concentrated to give the title compound (2.57 g, 100%) as a white foam. ES-LCMS *m/z* 336.26 (M+H).

Endo-1-[(1R,5S)-8-azabicyclo[3.2.1]oct-3-yl]-5-fluoro-2-methyl-1H-benzimidazole



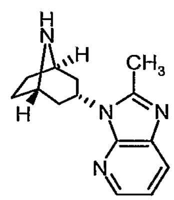
Endo-tert-butyl (1*R*,5*S*)-3-[(2-amino-4-fluorophenyl)amino]-8-azabicyclo[3.2.1]octane-8-carboxylate was treated with 1,1,1-triethoxyethane and a catalytic amount of camphor sulphonic acid at reflux for 3h. The reaction mixture was concentrated to dryness, redissolved in CH_3OH (10 mL), and treated with 6N HCl at reflux for 1h. The reaction mixture was concentrated to dryness, chased with EtOH, and triturated with EtOH to give a solid that was filtered and dried to give the di-HCl salt of *endo*-1-[(1*R*,5*S*)-8-azabicyclo[3.2.1]oct-3-yl]-5-fluoro-2-methyl-1*H*-benzimidazole as a grey solid. ES-LCMS *m/z* 260.27 (M+H).

Amine 6: *Endo-1-[(1R,5S)-8-azabicyclo[3.2.1]oct-3-yl]-4-fluoro-2-methyl-1H-benzimidazole*



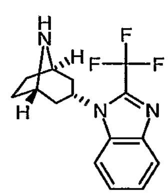
Prepared according to the method of Amine 5 from 1,3-difluoro-2-nitrobenzene. ES-LCMS *m/z* 260.24 (M+H).

Amine 7: *Endo-3-[(1R,5S)-8-azabicyclo[3.2.1]oct-3-yl]-2-methyl-3H-imidazo[4,5-b]pyridine*

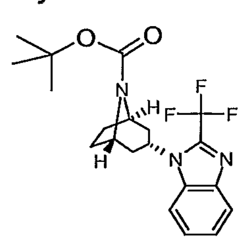


Prepared according to the method of Amine 5 from 2-chloro-3-nitropyridine. ES-LCMS *m/z* 243.22 (M+H).

Amine 8: *Endo-1-[(1R,5S)-8-azabicyclo[3.2.1]oct-3-yl]-2-(trifluoromethyl)-1H-benzimidazole*

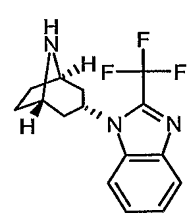


Endo-tert-butyl (1R,5S)-3-[2-(trifluoromethyl)-1H-benzimidazol-1-yl]-8-azabicyclo[3.2.1]octane-8-carboxylate



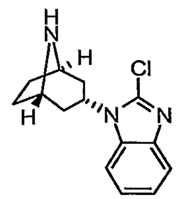
To a solution of trifluoroacetic acid (496 mg, 4.35 mmoles) in 5 mL DMF was added CDI (4.35 mmoles, 1 eq.) and stirred 30 min at ambient temperature until CO_2 evolution ceased. The reaction mixture was then cooled in an ice bath and *Endo-tert*-butyl 3-[(2-aminophenyl)amino]-8-azabicyclo[3.2.1] octane-8-carboxylate (WO 00/38680) (1.38 g, 4.35 mmoles, 1 eq.) dissolved in 10mL DMF was added slowly. The reaction mixture was stirred 30 min at 0°C and then warmed to ambient temperature and stirred for 30 min. The reaction mixture was then heated at 80°C for 16h. The reaction mixture was concentrated, dissolved in DCM, washed successively with saturated aqueous $NaHCO_3$ and water (3x). The organic phase was separated, dried over $MgSO_4$ and concentrated. A major impurity was removed by precipitation with Et_2O, filtered off, and the filtrate concentrated to dryness. The crude product was purified by normal phase flash chromatography (SiO_2, 10→40% EtOAc/Hexanes) to give *Endo-tert*-butyl (1*R*,5*S*)-3-[2-(trifluoromethyl)-1*H*-benzimidazol-1-yl]-8-azabicyclo[3.2.1]octane-8-carboxylate (0.36 g, 0.91 mmoles, 21%). ES-LCMS *m/z* 396.27 (M+H).

Endo-1-[(1R,5S)-8-azabicyclo[3.2.1]oct-3-yl]-2-(trifluoromethyl)-1H-benzimidazole

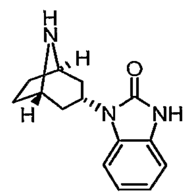


Endo-tert-butyl (1*R*,5*S*)-3-[2-(trifluoro-methyl)-1*H*-benzimidazol-1-yl]-8-azabicyclo [3.2.1]octane-8-carboxylate (330 mg, 0.84 mmoles) was dissolved in 6 mL DCM and treated with 4 mL 4N HCl in Dioxane at ambient temperature for 30 minutes. A solid precipitated from the reaction mixture and was filtered off to give the HCl salt of *Endo*-1-[(1*R*,5*S*)-8-azabicyclo[3.2.1]oct-3-yl]-2-(trifluoromethyl)-1*H*-benzimidazole (260 mg, 0.78 mmoles, 94%) as a pink solid. ES-LCMS *m/z* 295.67 (M+H).

Amine 9: *Endo-1-[(1R,5S)-8-azabicyclo[3.2.1]oct-3-yl]-2-chloro-1H-benzimidazole*

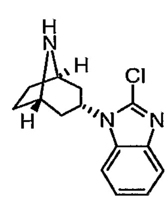


Endo-1-[(1R,5S)-8-azabicyclo[3.2.1]oct-3-yl]-1,3-dihydro-2H-benzimidazol-2-one



The title compound was obtained as a major by-product of the reaction of *Endo-tert*-butyl 3-[(2-aminophenyl)amino]-8-azabicyclo[3.2.1]octane-8-carboxylate (WO 00/38680) (1.7 g, 5.36 mmol) with 1-(triethoxymethoxy)ethane (5 mL) at 150 °C for 3h, followed by concentration, dissolution in CH_3OH (10 mL), and treatment with 6 N HCl at reflux for 1h. The reaction mixture was concentrated to dryness, chased with EtOH, and triturated with EtOH to give a solid that was filtered and dried to give the HCl salt of *Endo*-1-[(1*R*,5*S*)-8-azabicyclo[3.2.1]oct-3-yl]-1,3-dihydro-2*H*-benzimidazol-2-one (0.73 g, 3.00 mmoles, 56%). ES-LCMS *m/z* 244.00 (M+H).

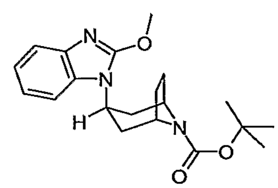
Endo-1-[(1R,5S)-8-azabicyclo[3.2.1]oct-3-yl]-2-chloro-1H-benzimidazole



Endo-1-[(1*R*,5*S*)-8-azabicyclo[3.2.1]oct-3-yl]-1,3-dihydro-2*H*-benzimidazol-2-one (0.73 g, 3.00 mmoles) was treated with 5 mL $POCl_3$ with

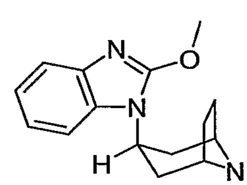
a catalytic amount of DMAP at reflux for 12h. The reaction was cooled and quenched with slow addition of 6N NaOH until pH was basic. The reaction mixture was extracted with DCM, dried over $MgSO_4$, filtered and concentrated to give impure *Endo*-1-[(1*R*,5*S*)-8-azabicyclo[3.2.1]oct-3-yl]-2-chloro-1*H*-benzimidazole as a tan foam. The crude amine was used as is. ES-LCMS *m/z* 262.23 (M+H).

Amine 10: *Endo-1-(8-azabicyclo[3.2.1]oct-3-yl)-2-methoxy-1H-benzimidazole*
Endo-tert-butyl 3-(2-methoxy-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate



Endo-tert-butyl 3-[(2-aminophenyl)amino]-8-azabicyclo[3.2.1]octane-8-carboxylate (WO 00/38680) (1.0 g, 3.15 mmol) was treated with 5 mL tetramethyl orthocarbonate at reflux for 40h. The reaction mixture was concentrated to dryness and purified by flash chromatography on silica gel eluted with 20% EtOAc in hexanes to give *Endo-tert*-butyl 3-(2-methoxy-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate (0.50 g, 1.40 mmol, 44%) as an orange oil. ES-LCMS *m/z* 358.11 (M+H).

Endo-1-(8-azabicyclo[3.2.1]oct-3-yl)-2-methoxy-1H-benzimidazole

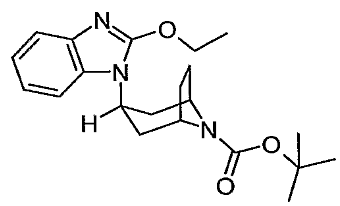


Tert-butyl 3-(2-methoxy-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate (0.50 g, 1.40 mmol) suspended in DCM (2 mL) was treated with TFA (1 mL) at ambient temperature for 5 min. The reaction mixture was concentrated to dryness and the product was crystalized from EtOAc/Et_2O to give the di-TFA salt of *Endo*-1-(8-azabicyclo[3.2.1]oct-3-

yl)-2-methoxy-1*H*-benzimidazole (340 mg, 0.722 mmol, 51%) as a tan solid. ^{1}H NMR (300 MHz, D_2O) δ 7.35 (m, 1H), 7.26 (m, 1H), 7.12 (m, 2H), 4.65 (m, 1H), 4.08-4.00 (m, 2H), 4.03 (s, 3H), 2.55-2.45 (m, 2H), 2.17-2.02 (m, 6H). ES-LCMS *m/z* 258.02 (M+H).

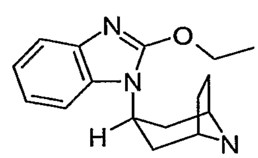
Amine 11: *Endo-1-(8-azabicyclo[3.2.1]oct-3-yl)-2-ethoxy-1H-benzimidazole*

Endo-tert-butyl 3-(2-ethoxy-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate



Endo-tert-butyl 3-[(2-aminophenyl)amino]-8-azabicyclo[3.2.1]octane-8-carboxylate (WO 00/38680) (1.7 g, 5.36 mmol) was treated with 10 mL tetraethyl orthocarbonate at reflux for 16h. The reaction mixture was concentrated to dryness and purified by flash chromatography on silica gel eluted with DCM followed by 20% EtOAc in Hexanes to give *Endo-tert*-butyl 3-(2-ethoxy-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate (1.15 g, 3.10 mmol, 58%) as an amber oil. ES-LCMS *m/z* 372.19 (M+H).

Endo-1-(8-azabicyclo[3.2.1]oct-3-yl)-2-ethoxy-1H-benzimidazole

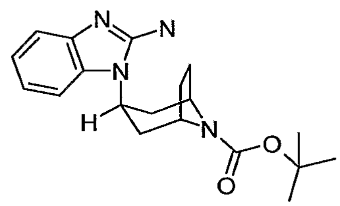


Endo-tert-butyl 3-(2-ethoxy-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate (1.15 g, 3.10 mmol) suspended in DCM (4 mL) was treated with TFA (1 mL) at ambient temperature for 5 min. The reaction mixture was concentrated to dryness and the product crystalized from EtOAc/Et_2O to give the di-TFA salt of *Endo*-1-(8-azabicyclo[3.2.1]oct-3-yl)-2-ethoxy-1*H*-benzimidazole (715 mg, 1.43 mmol, 46%) as a white powder. ^{1}H NMR (300 MHz, D_2O) δ 7.36 (m, 1H), 7.27 (m, 1H), 7.12 (m, 2H), 4.65 (m,

1H), 4.43 (q, 2H, J=7.1 Hz), 4.00 (m, 2H), 2.54-2.43 (m, 2H), 2.16-2.00 (m, 6H). ES-LCMS *m/z* 272.05 (M+H).

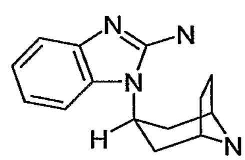
Amine 12: *Endo-1-(8-azabicyclo[3.2.1]oct-3-yl)-1H-benzimidazol-2-amine*

Endo-tert-butyl 3-(2-amino-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate



Endo-tert-butyl 3-[(2-aminophenyl)amino]-8-azabicyclo[3.2.1]octane-8-carboxylate (WO 00/38680) (2.5 g, 7.88 mmol) was treated with BrCN (0.92 g, 8.66 mmol) in CH_3OH (30 mL) at reflux for 3h and concentrated to give *endo-tert*-butyl 3-(2-amino-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate (2.30 g, 6.73 mmol, 85%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.15 (d, 2H, J = 7.6 Hz), 6.97-6.86 (m, 2H), 6.21 (s, 2H), 4.34 (m, 2H), 4.22 (pent, 1H), 2.42-2.32 (m, 2H), 1.98-1.85 (m, 6H), 1.44 (s, 9H). ES-LCMS *m/z* 343.12 (M+H).

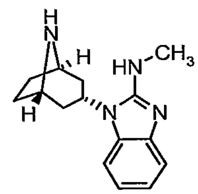
Endo-1-(8-azabicyclo[3.2.1]oct-3-yl)-1H-benzimidazol-2-amine



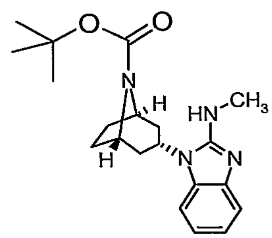
Endo-tert-butyl 3-(2-amino-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate (0.244 g, 0.713 mmol) suspended in DCM (2 mL) was treated with TFA (2 mL) at ambient temperature for 30 min. The reaction mixture was concentrated to dryness and the product crystalized from EtOAc to give the di-TFA salt of *Endo*-1-(8-azabicyclo[3.2.1]oct-3-yl)-1*H*-benzimidazol-2-amine (320 mg, 0.681 mmol, 95%) as a white solid. ^{1}H NMR

(300 MHz, D_2O) δ 7.40-7.20 (m, 4H), 4.66-4.49 (m, 1H), 4.16 (m, 2H), 2.71-2.60 (m, 2H), 2.29-2.11 (m, 6H). ES-LCMS *m/z* 243.04 (M+H).

Amine 13: *Endo-1-[(1R,5S)-8-azabicyclo[3.2.1]oct-3-yl]-N-methyl-1H-benzimidazol-2-amine*

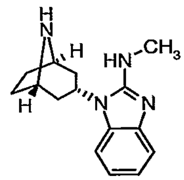


Endo-tert-butyl (1R,5S)-3-[2-(methylamino)-1H-benzimidazol-1-yl]-8-azabicyclo[3.2.1]octane-8-carboxylate



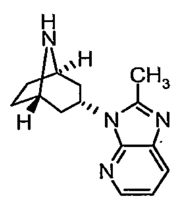
Endo-tert-butyl 3-[(2-aminophenyl)amino]-8-azabicyclo[3.2.1]octane-8-carboxylate (WO 00/38680) (900 mg, 2.83 mmol) in THF was treated with methyl isothiocyanate (230 mg, 3.15 mmoles, 1.1 eq.) at 0°C for 1h followed by 16h at ambient temperature. The reaction mixture was concentrated, redissolved in 7mL DMF and treated with 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (815 mg, 1.5 eq.) at ambient temperature for 16h. The reaction mixture was concentrated, dissolved in EtOAc, washed successively with saturated aqueous $NaHCO_3$, water (3x), and brine. The organic phase was separated, dried over $MgSO_4$ and concentrated to give the desired product, *endo-tert*-butyl (1*R*,5*S*)-3-[2-(methylamino)-1*H*-benzimidazol-1-yl]-8-azabicyclo[3.2.1]octane-8-carboxylate. ES-LCMS *m/z* 357.15 (M+H).

Endo-1-[(1R,5S)-8-azabicyclo[3.2.1]oct-3-yl]-N-methyl-1H-benzimidazol-2-amine

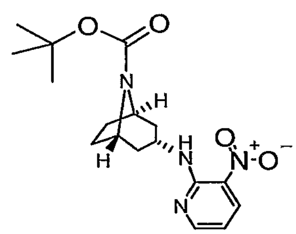


Endo-tert-butyl (1*R*,5*S*)-3-[2-(methylamino)-1*H*-benzimidazol-1-yl]-8-azabicyclo[3.2.1]octane-8-carboxylate was dissolved in 3 mL CH_3OH and treated with 3 mL 4N HCl in Dioxane at ambient temperature for 30 minutes. The reaction mixture was concentrated and triturated with EtOH, filtered, and dried to give the di-HCl salt of *Endo*-1-[(1*R*,5*S*)-8-azabicyclo[3.2.1]oct-3-yl]-*N*-methyl-1*H*-benzimidazol-2-amine (201 mg, 0.61 mmoles, 60%) as a pink solid. ES-LCMS *m/z* 257.04 (M+H).

Amine 14: *Endo-3-[(1R,5S)-8-azabicyclo[3.2.1]oct-3-yl]-2-methyl-3H-imidazo[4,5-b]pyridine*



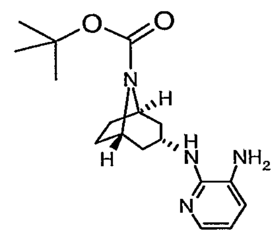
Endo-tert-butyl (1R,5S)-3-[(3-nitropyridin-2-yl)amino]-8-azabicyclo[3.2.1]octane-8-carboxylate



Endo-tert-butyl (1*R*,5*S*)-3-amino-8-azabicyclo[3.2.1]octane-8-carboxylate (WO 00/38680) (8.64 g, 38.3 mmoles) was treated with 2-chloro-3-nitropyridine (6.08 g, 1 eq.) in 50 mL NMP with DIPEA (10.9 g, 2.2 eq.) at 70°C for 16h. The reaction mixture was cooled to ambient temperature, and water (60 mL) added to incipient cloudiness. The reaction mixture was stirred until a heavy precipitate formed. The precipitate was filtered off, washed successively with NMP/water (1:1) and water, and air dried to give *endo-tert-*

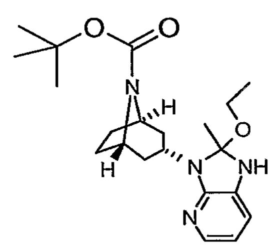
butyl (1*R*,5*S*)-3-[(3-nitropyridin-2-yl)amino]-8-azabicyclo[3.2.1]octane-8-carboxylate as an brown solid (11.5 g, 33.0 mmoles, 86%).

Endo-tert-butyl (1R,5S)-3-[(3-aminopyridin-2-yl)amino]-8-azabicyclo[3.2.1]octane-8-carboxylate



Endo-tert-butyl (1*R*,5*S*)-3-[(3-nitropyridin-2-yl)amino]-8-azabicyclo[3.2.1]octane-8-carboxylate (5.17 g, 14.8 mmoles) was subjected to catalytic hydrogenation with 10% Pd/C (500 mg) in EtOH/EtOAc (1:1, 200 mL) under 1 atm H_2(g) for 16h. The catalyst was filtered off and the filtrate was concentrated to give *Endo-tert*-butyl (1*R*,5*S*)-3-[(3-aminopyridin-2-yl)amino]-8-azabicyclo[3.2.1]octane-8-carboxylate as a brown foam and was used in the next step without further characterization.

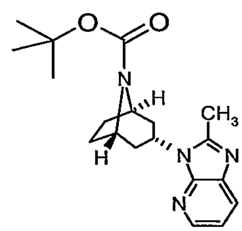
Endo-tert-butyl (1R,5S)-3-(2-ethoxy-2-methyl-1,2-dihydro-3H-imidazo[4,5-b]pyridin-3-yl)-8-azabicyclo [3.2.1]octane-8-carboxylate



Endo-tert-butyl (1*R*,5*S*)-3-[(3-aminopyridin-2-yl)amino]-8-azabicyclo[3.2.1]octane-8-carboxylate (2.85 g, 8.52 mmoles) was treated with 1,1,1-triethoxyethane and a catalytic amount of camphor sulphonic acid at reflux for 3h. The reaction mixture was concentrated to dryness, dissolved in EtOAc, washed with saturated aqueous $NaHCO_3$, the organic phase separated, dried over $MgSO_4$, filtered and concentrated. The crude product was purified by normal phase flash chromatography (SiO_2, 10→40%

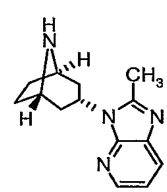
EtOAc/Hexanes) to give *endo-tert*-butyl (1*R*,5*S*)-3-(2-ethoxy-2-methyl-1,2-dihydro-3*H*-imidazo[4,5-*b*] pyridin-3-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate (2.66 g, 6.84 mmoles, 80%). ES-LCMS *m/z* 411.08 (M+Na).

Endo-tert-butyl (1R,5S)-3-(2-methyl-3H-imidazo[4,5-b]pyridin-3-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate



Endo-tert-butyl (1*R*,5*S*)-3-(2-ethoxy-2-methyl-1,2-dihydro-3*H*-imidazo[4,5-*b*]pyridin-3-yl)-8-azabicyclo [3.2.1]octane-8-carboxylate (2.66 g, 6.84 mmoles) and a catalytic amount of camphor sulphonic acid were combined in NMP at 150 °C for 12h. The reaction mixture was cooled to ambient temperature, diluted with EtOAc, washed successively with saturated aqueous $NaHCO_3$ and brine (5x). The organic phase was separated, dried over $MgSO_4$, filtered and concentrated. The crude product was purified by normal phase flash chromatography (SiO_2, EtOAc) to give *Endo-tert*-butyl (1*R*,5*S*)-3-(2-methyl-3*H*-imidazo[4,5-*b*]pyridin-3-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate (1.60 g, 4.67 mmoles, 68%). ES-LCMS *m/z* 343.24 (M+H).

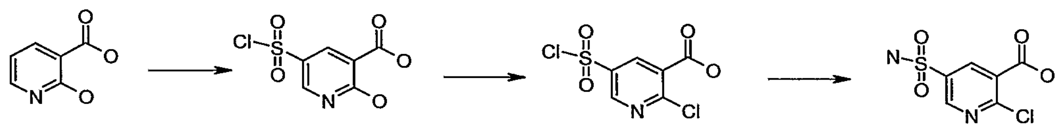
Endo-3-[(1R,5S)-8-azabicyclo[3.2.1]oct-3-yl]-2-methyl-3H-imidazo[4,5-b]pyridine



Endo-tert-butyl (1*R*,5*S*)-3-(2-methyl-3*H*-imidazo[4,5-*b*]pyridin-3-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate (1.60 g, 4.67 mmoles) was dissolved in 15 mL DCM and treated with 4 N HCl in dioxane at ambient temperature for 30 min. A precipitate formed directly from the reaction mixture and was

filtered and dried to give the HCl salt of *Endo*-3-[(1*R*,5*S*)-8-azabicyclo [3.2.1]oct-3-yl]-2-methyl-3*H*-imidazo[4,5-*b*]pyridine as a brown solid. ES-LCMS *m/z* 243.22 (M+H).

Synthesis of the 5-(aminosulfonyl)-2-chloronicotinic acid

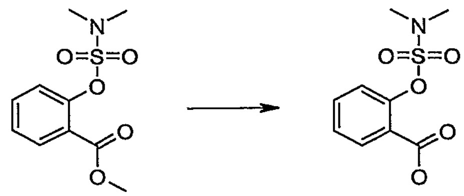


2-Hydroxynicotinic acid (10.0 g, 71.8 mmol) was dissolved in 25 ml of chlorosulfonic acid and heated to 160°C overnight. After cooling the reaction was slowly poured into ice and stirred in an ice bath until a white precipitate formed. The solid was filtered off and dried under vacuum to afford 7.55 g of 5-(chlorosulfonyl)-2-hydroxynicotinic acid (44% yield). 1H NMR (300 MHz, DMSO-d6) δ ppm 7.9 (dd, *J*=2.5, 0.7Hz, 1H) 8.4 (dd, *J*=2.6, 0.7Hz, 1H).

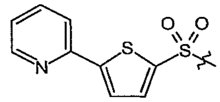
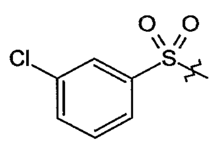
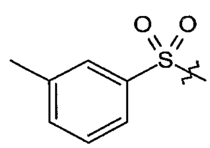
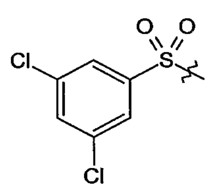
5-(Chlorosulfonyl)-2-hydroxynicotinic acid (500 mg, 2.10 mmol) vas suspended in 5 ml of $POCl_3$ in a sealed tube and heated to 130 °C until all solid had dissolved. The reaction was cooled to 0 °C and poured onto ice and stirred until a solid formed. The filtered white solid was dried to afford 2-chloro-5-(chlorosulfonyl)nicotinic acid. ^{1}H NMR (400 MHz, Acetone-d6) δ ppm 8.9 (d, *J*=2.6Hz, 10H), 9.3 (d, *J*=2.6Hz, 10H).

2-Chloro-5-(chlorosulfonyl)nicotinic acid (400 mg, 1.56 mmol) was stirred in a slurry of ice and excess ammonium hydroxide was added at 0°C and stirred untill all of the ice had melted. The resulting solution was evaporated to afford a white solid 5-(aminosulfonyl)-2-chloronicotinic acid. MS ES+ 237 (M+H). ^{1}H NMR (400 MHz, DMSO-D6) δ ppm 8.1 (dd, *J*=2.6, 0.9Hz, 1H), 8.6 (m, 1H).

2-{[(dimethylamino)sulfonyl]oxy}benzoic acid

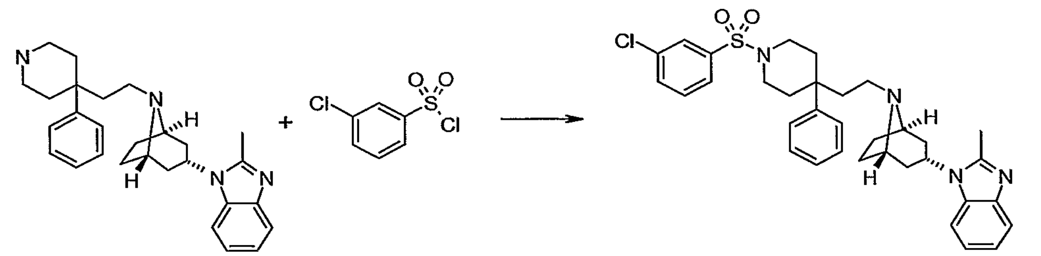


Methyl 2-{[(dimethylamino)sulfonyl]oxy} benzoate (325.0 mg, 1.253 mmol) was dissolved in 2 ml of 1,4-dioxane and 2 ml of 1M LiOH was added. The resulting solution was shaken overnight at 45°C. The reaction mixture was washed with DCE and separated using a hydrophobic frit. The aqueous layer was acidified to give a white solid which was filtered and dried to afford 244.4 mg (80% yield) of 2-{[(dimethyl-amino)sulfonyl]oxy}benzoic acid.

Example	Acid source	R	X	Y	% yield	LCMS result	ion	Method
Example 385	Commercial		H	C	34	652	(M+H)	sulfonyl
Example 386	Commercial		H	C	21	603	(M+H)	sulfonyl
Example 343	Commercial		H	C	41	583	(M+H)	sulfonyl
Example 387	Commercial		H	C	74	637	(M+H)	sulfonyl

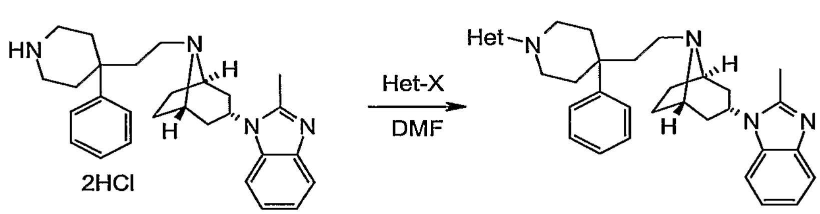
Example 386

1-[(1R,5S)-8-(2-{1-[(3-chlorophenyl)sulfonyl]-4-phenyl-4-piperidinyl}ethyl)-8-azabicyclo[3.2.1]oct-3-yl]-2-methyl-1H-benzimidazole



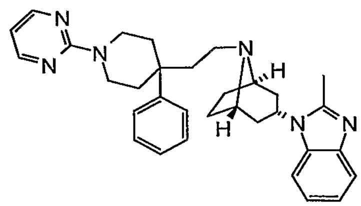
3-Chlorobenzenesulfonyl chloride (31.6 mg, 0.122 mmol) was added to a solution of 2-methyl-1-{(1*R*,5*S*)-8-[2-(4-phenyl-4-piperidinyl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1*H*-benzimidazole (50.0 mg, 0.117 mmol) and diisopropyletheylamine (44.9 mg, 0.348 mmol) in DCM. The reactions were quenched with sat. $NaHCO_3$ and separated with a hydrophobic frit. Flash chromatography on silica 0 to 10% MeOH in EtOAc afforded 1-[(1*R*,5*S*)-8-(2-{1-[(3-chlorophenyl)sulfonyl]-4-phenyl-4-piperidinyl}ethyl)-8-azabicyclo[3.2.1]oct-3-yl]-2-methyl-1*H*-benzimidazole 14.7 mg (20% yield). MS ES+ 603(M+H). ^{1}H NMR (300 MHz, chloroform-d) δ ppm 1.6 (m, 2H), 1.7 (m, 4H), 1.9 (m, 8H), 2.4 (m, 4H), 2.6 (s, 3H), 2.8 (m, 2H), 3.4 (m, 2H), 4.6 (m, 1H), 7.2 (m, 5H), 7.3 (m, 3H), 7.4 (t, *J*=7.9Hz, 1H), 7.5 (m, 1H), 7.6 (d, *J*=7.8Hz, 1H), 7.7 (m, 1H), 7.7 (m, *J*=1.8, 1.8Hz, 1H).

General Scheme Towards Pyrimidinyl and Tetrahydro-biimidazolyl Derivatives of 2-Methyl-1-{8-[2-(4-Phenylpiperidin-4-yl)ethyl]-8-Azabicyclo[3.2.1]oct-3-yl}-1H-Benzimidazole



Example 388

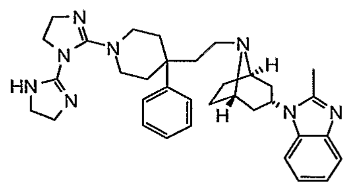
Preparation of 2-methyl-1-{8-[2-(4-phenyl-1-pyrimidin-2-ylpiperidin-4-yl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1H-benzimidazole



To a stirred solution of 2-methyl-1-{8-[2-(4-phenylpiperidin-4-yl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1*H*-benzimidazole dihydrochloride (25.3 mg, 0.05 mmol) in *N, N*-dimethylformade (2 mL) was added 2-chloropyrimidine (8.6 mg, 0.075 mmol) and triethylamine (21 μL, 0.15 mmol). The resulting mixture was stirred at 80 °C for 2.5 hours. After evaporation of the solvent, the crude product was directly purified by flash chromatography on silical gel, eluting with a gradient of 0-10% triethylamine in methanol to afford 2-methyl-1-{8-[2-(4-phenyl-1-pyrimidin-2-ylpiperidin-4-yl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1*H*-benzimidazole as amorphous solid (16.2 mg, 65%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.30 (d, J=6.0Hz, 2H), 7.67 (dd, J=2.6, 7.0Hz, 1H), 7.39-7.37 (m, 4H), 7.35-7.22 (m, 3H), 7.21-7.14 (m, 2H), 6.45 (t, J= 4.7Hz, 1H), 4.64 (m, 1H), 4.17-4.09 (m, 2H), 3.61-3.52 (m, 2H), 3.28-3.25 (m, 2H), 2.59 (s, 3H), 2.44-2.33 (m, 2H), 2.29-2.22 (m, 2H), 1.97-1.85 (m, 10H), 1.62 (d, J=7.7Hz, 2H). HRMS *m/z* $(M+H)^+$ calcd: 507.3236; obsd: 507.3248.

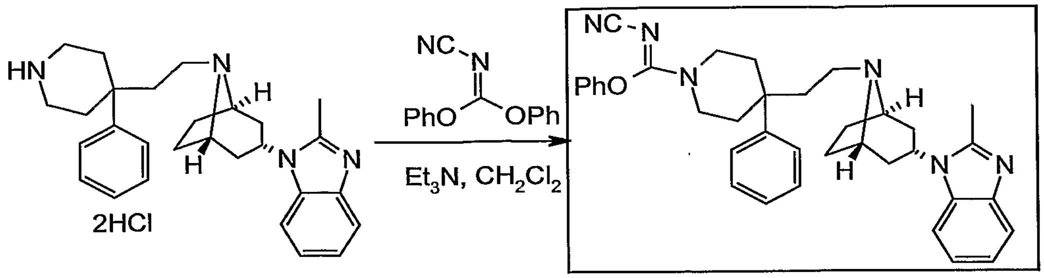
Example 389

Preparation of 2-methyl-1-(8-{2-[4-phenyl-1-(4,4',5,5'-tetrahydro-1'H-1,2'-biimidazol-2-yl)piperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-1H-benzimidazole

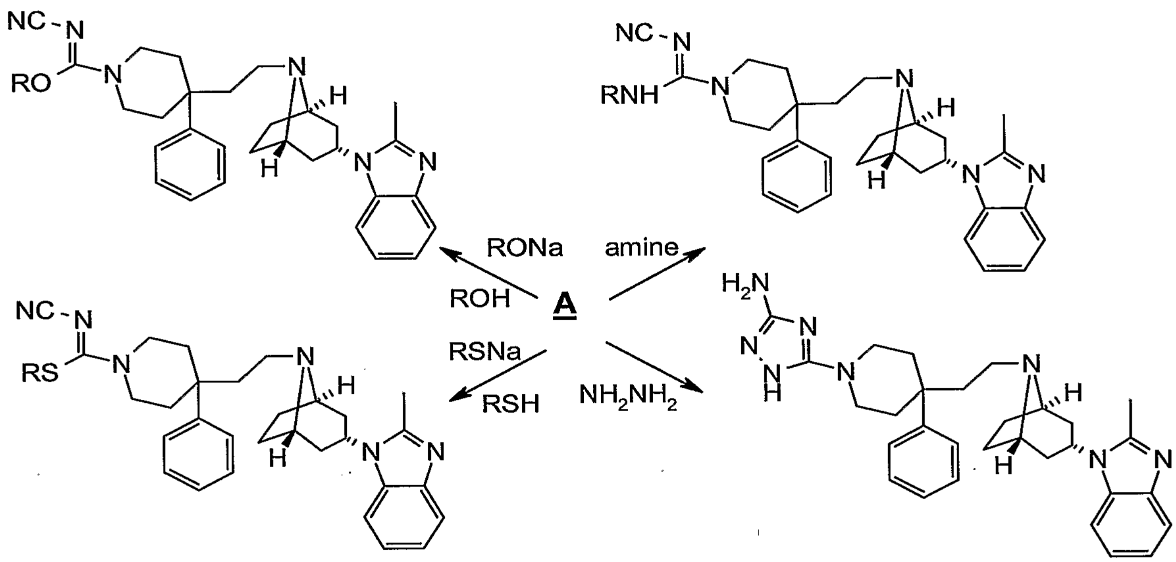


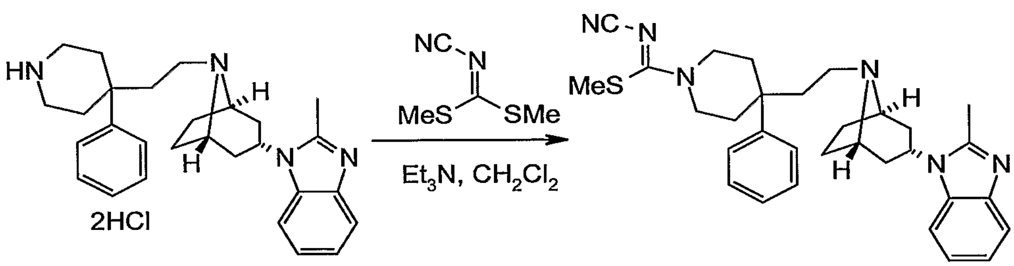
2-Methyl-1-(8-{2-[4-phenyl-1-(4,4',5,5'-tetrahydro-1'*H*-1,2'-biimidazol-2-yl)piperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-1*H*-benzimidazole (16 mg, 58%) was obtained as amorphous solid from 2-methyl-1-{8-[2-(4-phenylpiperidin-4-yl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1*H*-benzimidazole dihydrochloride (25.3 mg, 0.05 mmol) and 2-methylthio-2-imidazoline hydroiodide (24.4 mg, 0.1 mmol) by the similar procedure outlined in example 388. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.68-7.65 (m, 1H), 7.40-7.35 (m, 2H), 7.31-7.25 (m, 4H), 7.21-7.12 (m, 2H), 5.87 (br, 1H), 4.65-4.58 (m, 1H), 4.06-3.97 (m, 2H), 3.17-3.65 (m, 6H), 3.32-3.26 (m, 4H), 3.12-3.06 (m, 2H), 2.58 (s, 3H), 2.42-2.32 (m, 2H), 2.25-2.19 (m, 2H), 1.97-1.86 (m, 10H), 1.62 (d, J=7.9Hz, 2H). HRMS *m/z* $(M+H)^+$ calcd: 565.3767, obsd: 565.3755.

Preparation of Carboximidoate, Carboximidamide and Carbimdo-thioate Derivatives of 2-Methyl-1-{8-[2-(4-Phenylpiperidin-4-yl)ethyl] –8-Azabicyclo-[3.2.1]oct-3-yl}-1H-Benzimidazole



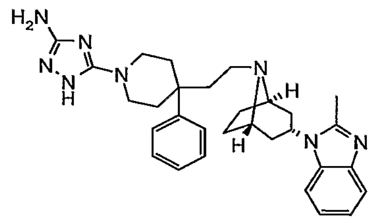
A





Example 390

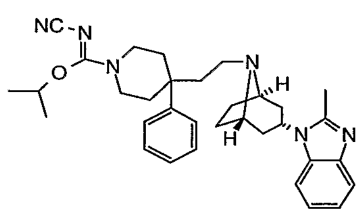
Preparation of 5-(4-{2-[3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo [3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)-1H-1,2,4-triazol-3-amine



To a stirred solution of phenyl *N*-cyano-4-{2-[3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1] oct-8-yl]ethyl}-4-phenylpiperidine-1-carboximidoate (18 mg, 0.031 mmol) in isopropyl alcohol (1 mL) was added hydrazine (3.6 μL, 0.11 mmol). The resulting mixture was then stirred at 80 °C for 4 hours. After evaporation of the solvents, the residue was purified by flash chromatography to afford 5-(4-{2-[3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)-1*H*-1,2,4-triazol-3-amine as white solid (12.5 mg, 79%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.67-7.64 (m, 2H), 7.39-7.29 (m, 5H), 7.25-7.13 (m, 3H), 4.66-4.55 (m, 2H), 4.28 (br, 2H), 3.56-3.49 (m, 3H), 3.27-3.21 (m, 4H), 2.57 (s, 3H), 2.42-2.22 (m, 4H), 1.96-1.82 (m, 9H), 1.64-1.62 (m, 2H). HRMS *m/z* $(M+H)^+$ calcd: 511.3298, obsd: 511.3289.

Example 391

Preparation of isopropyl N-cyano-4-{2-[3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidine-1-carboximidoate

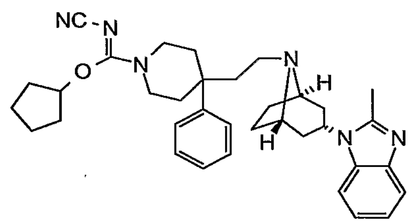


Isopropyl *N*-cyano-4-{2-[3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidine-1-carboximidoate (13 mg, 92%) was obtained as amorphous solid from phenyl *N*-cyano-4-{2-[3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1] oct-8-yl]ethyl}-4-phenylpiperidine-1-carboximidoate (15 mg, 0.026 mmol) and sodium isopropoxide by the similar procedure outlined in example 7. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.67 (d, J=7.0Hz, 1H), 7.42-7.35 (m, 2H), 7.29-7.21 (m, 4H),

7.19-7.13 (m, 2H), 5.30-5.22 (m, 1H), 4.69 (br, 1H), 4.14-4.02 (m, 2H), 3.38-3.20 (m, 4H), 2.59 (s, 3H), 2.41-2.14 (m, 4H), 1.94-1.68 (m, 12H), 1.32 (d, J=6.2Hz, 6H). HRMS *m/z* $(M+H)^+$ calcd: 539.3498, obsd: 539.3503.

Example 392

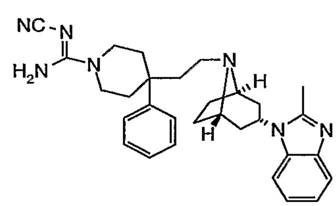
Preparation of cyclopentyl N-cyano-4-{2-[3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidine-1-carboximidoate



Cyclopentyl *N*-cyano-4-{2-[3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidine-1-carboximidoate (15 mg, 81%) was obtained from phenyl *N*-cyano-4-{2-[3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidine-1-carboximidoate (19 mg, 0.033 mmol) and sodium cyclopentoxide by the similar procedure outlined in example 7. ^1H NMR ($CDCl_3$, 300 MHz): δ 7.67 (d, J=6.9Hz, 1H), 7.42-7.31 (m, 2H), 7.29-7.24 (m, 4H), 7.19-7.12 (m, 2H), 5.51-5.47 (m, 1H), 4.68 (br, 1H), 3.99 (br, 2H), 3.35-3.28 (m, 4H), 2.59 (s, 3H), 2.42-2.28 (m, 4H), 1.97-1.81 (m, 14H), 1.75-1.62 (m, 6H). HRMS *m/z* $(M+H)^+$ calcd: 565.3655, obsd: 565.3663.

Example 393A

Preparation of N'-cyano-4-{2-[3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo-[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidine-1-carboximidamide

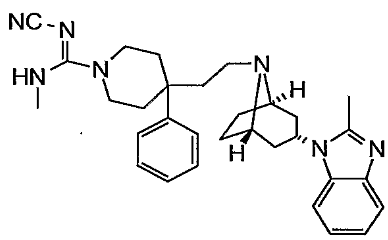


Phenyl *N*-cyano-4-{2-[3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidine-1-carboximidoate (100 mg,

0.175 mmol) and a solution of ammonia in methanol (2 mL, 1.4 M) was stirred at ambient temperature for 20 hours. After evaporation of the excess ammonia and the solvent, the residue was subject to flash chromatography (Mega Bond Elut Si, MeOH/EtOAc, 10% to 40%) to afford *N'*-cyano-4-{2-[3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidine-1-carboximidamide as amorphous solid (79 mg, 91%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.68-7.65 (m, 1H), 7.42-7.34 (m, 2H), 7.30-7.24 (m, 4H), 7.20-7.18 (m, 2H), 6.11 (s, 2H), 4.65 (t, J=8.5Hz, 1H), 3.82-3.78 (m, 2H), 3.27-3.20 (m, 4H), 2.53 (s, 3H), 2.45-2.25 (m, 4H), 1.96-1.84 (m, 10H), 1.64 (d, J=7.5Hz, 2H). HRMS *m/z* $(M+H)^+$ calcd: 496.3189, obsd: 496.3181.

<u>Example 393B</u>

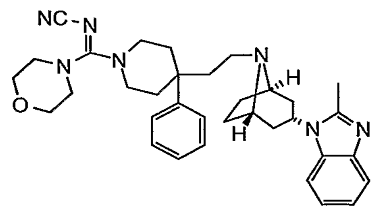
<u>Preparation of N'-cyano-N-methyl-4-{2-[3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidine-1-carboximidamide</u>



N'-cyano-*N*-methyl-4-{2-[3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidine-1-carboximidamide (18 mg, quant.) was obtained from phenyl *N*-cyano-4-{2-[3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidine-1-carboximidoate (20 mg, 0.035 mmol) and methylamine (0.7 mL, 2 M in EtOH) by the similar procedure outlined in example 393. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.69 (d, J=7.3Hz, 1H), 7.44-7.39 (m, 2H), 7.32-7.25 (m, 4H), 7.22-7.16 (m, 2H), 5.37 (s, 1H), 4.83 (br, 1H), 3.80-3.76 (m, 2H), 3.35-3.24 (m, 4H), 3.03 (d, J=4.6Hz, 3H), 2.63 (s, 3H), 2.56-2.29 (m, 4H), 2.08-1.89 (m, 10H), 1.73-1.71 (m, 2H). HRMS *m/z* $(M+H)^+$ calcd: 510.3345, obsd: 510.3348.

Example 394

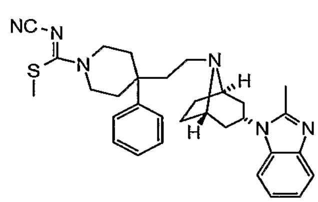
Preparation of (4-{2-[3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)(morpholin-4-yl)methylidene-cyanamide



(4-{2-[3-(2-Methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)(morpholin-4-yl)methylidenecyanamide (5.1 mg, 26%) was obtained from phenyl *N*-cyano-4-{2-[3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidine-1-carboximidoate (20 mg, 0.035 mmol) and morpholine (2 mL) by the similar procedure outlined in example 393. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.67 (d, J=7.5Hz, 1H), 7.41-7.37 (m, 2H), 7.29-7.25 (m, 4H), 7.21-7.13 (m, 2H), 3.71-3.63 (m, 7H), 3.44-3.30 (m, 7H), 2.64 (s, 3H), 2.32-2.16 (m, 4H), 1.98 (br, 8H), 1.69 (br, 6H). HRMS *m/z* $(M+H)^+$ calcd: 566.3607, obsd: 566.3610.

Example 395

Preparation of methyl N-cyano-4-{2-[3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidine-1-carbimidothioate

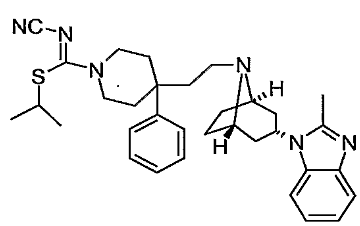


To a stirred solution of 2-methyl-1-{8-[2-(4-phenylpiperidin-4-yl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1*H*-benzimidazole dihydrochloride (25.3 mg, 0.05 mmol) in dichloromethane (2 mL) was added triethylamine (14 μL, 1 mmol) and dimethylcyanodithioiminocarbonate (8.8 mg, 0.06 mmol). The resulting mixture was stirred at ambient temperature for 3 hours before it was quenched with saturated sodium bicarbonate solution. The layers were

separated and the aqueous layer was extracted with dichloromethane (2 x 10 mL). The combined organic extracts were dried over anhydrous sodium sulfate. After evaporation of the solvent, the crude product was purified by flash chromatography on silical gel, eluting with a gradient of 0-15% methanol in ethyl acetate to afford methyl *N*-cyano-4-{2-[3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidine-1-carbimidothioate as amorphous solid (18 mg, 68%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70(d, J=7.0Hz, 1H), 7.46-7.37 (m, 2H), 7.33-7.28 (m, 4H), 7.24-7.16 (m, 2H), 4.72 (br, 1H), 4.29-4.24 (m, 2H), 3.46 (t, J=11.1Hz, 2H), 3.31 (br, 2H), 2.78 (s, 3H), 2.62 (s, 3H), 2.54-2.35 (m, 4H), 2.08-1.86 (m, 10H), 1.69 (d, J=7.7Hz, 2H). HRMS *m/z* $(M+H)^+$ calcd: 527.2957, obsd: 527.2933.

Example 396

Preparation of isopropyl N-cyano-4-{2-[3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidine-1-carbimidothioate

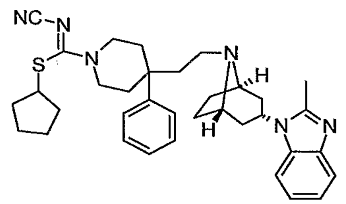


To a stirred solution of phenyl *N*-cyano-4-{2-[3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1] oct-8-yl]ethyl}-4-phenylpiperidine-1-carboximidoate (20 mg, 0.035 mmol) in THF (1 mL) was added sodium 2-propanethiolate (6.8 mg, 0.07 mmol). The resulting mixture was stirred at ambient temperature for 30 minutes before evaporation of the solvent. The crude product was then purified by flash chromatography on silical gel, eluting with a gradient of 0-10% methanol in ethyl acetate to afford isopropyl *N*-cyano-4-{2-[3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo [3.2.1] oct-8-yl]ethyl}-4-phenylpiperidine-1-carbimidothioate as a white solid (14 mg, 72 %). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.69 (d, J=7.5Hz, 1H), 7.45-7.40 (m, 2H), 7.32-7.24 (m, 4H), 7.21-7.14 (m, 2H), 4.39-4.26 (m, 3H), 3.53 (br, 4H), 2.65 (s, 3H),

2.33-2.05 (m, 4H), 1.99-1.85 (m, 13H), 1.38 (d, J=6.4Hz, 6H). HRMS *m/z* $(M+H)^+$ calcd: 555.3270, obsd: 555.3274.

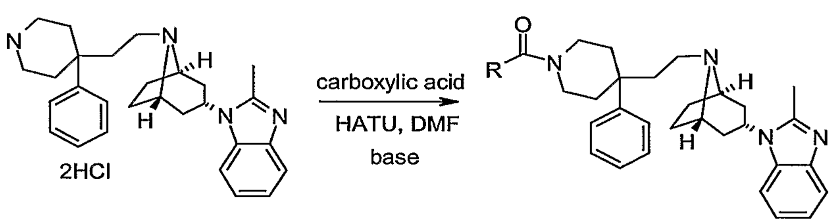
Example 397

Preparation of cyclopentyl N-cyano-4-{2-[3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidine-1-carbimidothioate



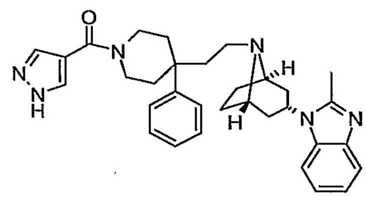
Cyclopentyl *N*-cyano-4-{2-[3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidine-1-carbimidothioate (20 mg, quant.) was obtained as amorphous solid from phenyl *N*-cyano-4-{2-[3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo [3.2.1]oct-8-yl]ethyl}-4-phenylpiperidine-1-carboximidoate (20 mg, 0.035 mmol) and sodium cyclopentanethiolate by the similar procedure outlined in example 396. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.68 (d, J=7.2Hz, 1H), 7.44-7.39 (m, 2H), 7.31-7.22 (m, 4H), 7.20-7.13 (m, 2H), 4.46-4.42 (m, 1H), 4.28-4.23 (m, 2H), 3.52-3.45 (m, 4H), 2.63 (s, 3H), 2.52 (br, 2H), 2.33-2.28 (m, 2H), 2.18-2.10 (m, 4H), 2.05-1.91 (m, 8H), 1.87-1.54 (m, 9H). HRMS *m/z* $(M+H)^+$ calcd: 581.3426, obsd: 581.3438.

Preparation of Amide Derivatives Through HATU Promoted Amidation Method



Example 398

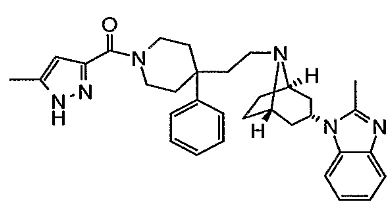
Preparation of 2-methyl-1-(8-{2-[4-phenyl-1-(1H-pyrazol-4-ylcarbonyl) piperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-1H-benzimidazole



2-Methyl-1-(8-{2-[4-phenyl-1-(1H-pyrazol-4-ylcarbonyl)piperidin-4-yl]ethyl}-8-azabicyclo[3.2.1] oct-3-yl)-1*H*-benzimidazole (27 mg, quant.) was obtained as amorphous solid from 2-methyl-1-{8-[2-(4-phenyl piperidin-4-yl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1*H*-benzimidazole dihydrochloride (25.3 mg, 0.05 mmol) and 4-pyrazoolecarboxylic acid (6 mg, 0.05 mmol) by the similar procedure outlined in example 5. ^{1}H NMR (300 MHz, DMSO-d_6 100°C) δ 7.84 (s, 2H), 7.54-7.51 (m, 1H), 7.47-7.38 (m, 5H), 7.28-7.24 (m, 1H), 7.18-7.11 (m, 2H), 3.91-3.86 (m, 3H), 3.46-3.40 (m, 4H), 3.08 (br, 3H), 2.53 (s, 3H), 2.16 (m, 2H), 2.08-1.74 (m, 12H). HRMS *m/z* $(M+H)^+$ calcd: 523.3185, obsd: 523.3195.

Example 399

Preparation of 2-methyl-1-[(1R,5S)-8-(2-{1-[(5-methyl-1H-pyrazol-3-yl)carbonyl]-4-phenylpiperidin-4-yl}ethyl)-8-azabicyclo[3.2.1]oct-3-yl]-1H-benzimidazole

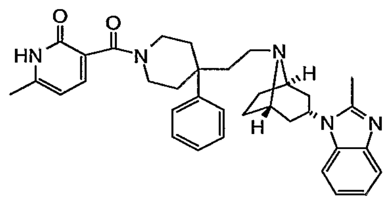


2-Methyl-1-[(1*R*, 5*S*)-8-(2-{1-[(5-methyl-1*H*-pyrazol-3-yl)carbonyl]-4-phenylpiperidin-4-yl}ethyl)-8-azabicyclo[3.2.1]oct-3-yl]-1*H*-benzimidazole (34 mg, 53%) was obtained as amorphous solid from 2-methyl-1-{8-[2-(4-phenylpiperidin-4-yl)ethyl]-8-azabicyclo [3.2.1]oct-3-yl}-1*H*-benzimidazole (51 mg, 0.12 mmol), 5-methyl-1*H*-pyrazole-3-carboxylic acid (15 mg, 0.12 mmol)

and HATU (47 mg, 0.12 mmol) by the similar procedure outlined in example 5. ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.78 (s, 1H), 7.49-7.47 (m, 1H), 7.38-7.33 (m, 4H), 7.23-7.21 (m, 1H), 7.11-7.05 (m, 3H), 6.24 (s, 1H), 4.50 (br, 1H), 4.12 (br, 1H), 3.86 (br, 1H), 3.60 (br, 1H), 3.23 (br, 3H), 2.45 (s, 3H), 2.39-2.32 (m, 2H), 2.23 (s, 3H), 2.09 (br, 2H), 1.97-1.71 (m, 10H), 1.58-1.55 (m, 2H). HRMS *m/z* $(M+H)^+$ calcd: 537.3342, obsd: 537.3367.

<u>Example 400</u>

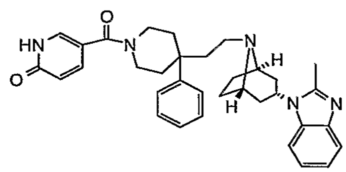
<u>Preparation of 6-methyl-3-[(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl] ethyl}-4-phenylpiperidin-1-yl)carbonyl]pyridin-2(1H)-one</u>



6-Methyl-3-[(4-{2-[(1*R*, 5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]pyridin-2(1*H*)-one (30 mg, 53%) was obtained as amorphous solid from 2-methyl-1-{8-[2-(4-phenylpiperidin-4-yl)ethyl]-8-azabicyclo [3.2.1]oct-3-yl}-1*H*-benzimidazole dihydrochloride (51 mg, 0.10 mmol), 2-hydroxyl-6-methylpyridine-3-carboxylic acid (15 mg, 0.10 mmol) and HATU (38 mg, 0.10 mmol) by the similar procedure outlined in example 5. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (d, J=7.5Hz, 1H), 7.65 (d, J=7.3Hz, 1H), 7.50-7.34 (m, 2H), 7.30-7.21 (m, 5H), 7.19-7.12 (m, 2H), 6.18 (d, J=7.5Hz, 1H), 4.66-4.56 (m, 1H), 4.14-4.07 (m, 1H), 3.88 (br, 2H), 3.25 (br, 3H), 2.56 (s, 3H), 2.40-2.08 (m, 8H), 1.93-1.84 (m, 10H), 1.61 (d, J=6.5Hz, 2H). HRMS *m/z* $(M+H)^+$ calcd: 564.3339, obsd: 564.3349.

Example 401

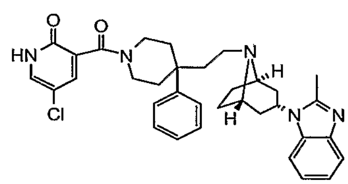
Preparation of 5-[(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]pyridin-2(1H)-one



5-[(4-{2-[(1*R*, 5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]pyridin-2(1*H*)-one (28 mg, 51 %) was obtained as amorphous solid from 2-methyl-1-{8-[2-(4-phenylpiperidin-4-yl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1*H*-benzimidazole dihydrochloride (51 mg, 0.10 mmol), 6-hydroxynicotinic acid (14 mg, 0.10 mmol) and HATU (38 mg, 0.10 mmol) by the similar procedure outlined in example 5. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66-7.62 (m, 2H), 7.54 (d, J=7.4Hz, 1H), 7.40-7.36 (m, 2H), 7.35-7.23 (m, 4H), 7.19-7.12 (m, 2H), 6.57 (d, J=9.6Hz, 1H), 4.64-4.59 (m, 1H), 3.88 (br, 2H), 3.34-3.25 (m, 4H), 2.56 (s, 3H), 2.41-2.20 (m, 4H), 1.93-1.82 (m, 10H), 1.62 (d, J=6.2Hz, 2H). HRMS *m/z* $(M+H)^+$ calcd: 550.3182, obsd: 550.3169.

Example 402

Preparation of 5-chloro-3-[(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl] ethyl}-4-phenylpiperidin-1-yl)carbonyl]pyridin-2(1H)-one

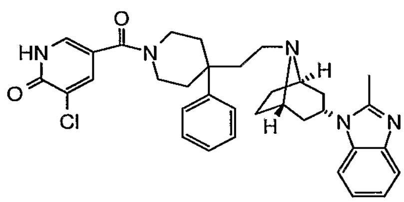


5-Chloro-3-[(4-{2-[(1*R*, 5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]pyridin-2(1*H*)-one (20 mg, 34%) was obtained as amorphous solid from 2-methyl-1-{8-[2-(4-phenylpiperidin-4-yl)ethyl]-8-azabicyclo [3.2.1]oct-3-yl}-1*H*-benzimidazole

dihydrochloride (51 mg, 0.10 mmol), 5-chloro-2-hydroxylpyridine-3-carboxylic acid (18 mg, 0.10 mmol) and HATU (38 mg, 0.10 mmol) by the similar procedure outlined in example 5. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (d, J=8.4Hz, 1H), 7.51-7.45 (m, 2H), 7.40-7.35 (m, 2H), 7.31-7.24 (m, 4H), 7.22-7.12 (m, 2H), 4.64-4.58 (m, 1H), 4.15-4.08 (m, 2H), 3.45-3.23 (m, 6H), 2.57 (s, 3H), 2.42-2.26 (m, 5H), 1.94-1.85 (m, 10H), 1.60 (d, J=6.8Hz, 2H). HRMS *m/z* $(M+H)^+$ calcd: 584.2792, obsd: 584.2785.

Example 403

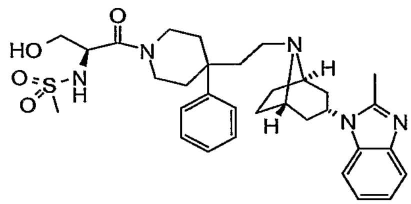
Preparation of 3-chloro-5-[(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]pyridin-2-(1H)-one



3-Chloro-5-[(4-{2-[(1*R*, 5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]pyridin-2(1*H*)-one (25 mg, 42%) was obtained as amorphous solid from 2-methyl-1-{8-[2-(4-phenylpiperidin-4-yl)ethyl]-8-azabicyclo [3.2.1]oct-3-yl}-1*H*-benzimidazole dihydrochloride (51 mg, 0.10 mmol), 5-chloro-6-hydroxylnicotinic acid (18 mg, 0.10 mmol) and HATU (38 mg, 0.10 mmol) by the similar procedure outlined in example 5. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (s, 1H), 7.66-7.63 (m, 2H), 7.41-7.38 (m, 2H), 7.35-7.24 (m, 4H), 7.19-7.12 (m, 2H), 4.64-4.59 (m, 1H), 3.89 (br, 2H), 3.35-3.26 (m, 4H), 2.57 (s, 3H), 2.41-2.28 (m, 4H), 1.94-1.83 (m, 11H), 1.62 (d, J=7.9 Hz, 2H). HRMS *m/z* $(M+H)^+$ calcd: 584.2792, obsd: 584.2787.

Example 404

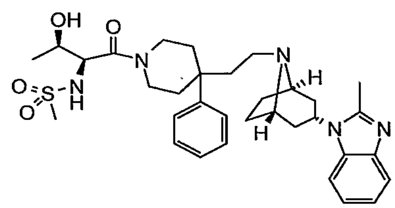
Preparation of (2S)-N[1],N[1]-bis{4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-[N-(methylsulfonyl)-L-seryl]-4-phenylpiperidin-2-yl}-N[2]-(methylsulfonyl)-L-serinamide



(2*S*)-*N*^{1},*N*^{1}-Bis{4-{2-[(1*R*, 5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-[*N*-(methylsulfonyl)-*L*-seryl]-4-phenylpiperidin-2-yl}-*N*^{2}-(methylsulfonyl)-*L*-serinamide (43 mg, 50 %) was obtained as amorphous solid from 2-methyl-1-{8-[2-(4-phenylpiperidin-4-yl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1*H*-benzimidazole dihydrochloride (70 mg, 0.14 mmol), *N*-(methylsulfonyl)-L-serine (28 mg, 0.15 mmol, prepared from *L*-serine and methanesulfonyl chloride) and HATU (57 mg, 0.15 mmol) by the similar procedure outlined in example 5. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (d, J=8.4Hz, 1H), 7.40-7.36 (m, 2H), 7.29-7.23 (m, 4H), 7.19-7.12 (m, 2H), 5.78 (dd, J=8.6, 16.5Hz, 1H), 4.63-4.58 (m, 1H), 4.56-4.45 (m, 1H), 4.09-4.04 (m, 1H), 3.85-3.65 (m, 3H), 3.40-3.09 (m, 4H), 3.02 (s, 3/2H), 2.90 (s, 3/2H), 2.57 (s, 3H), 2.41-2.20 (m, 5H), 1.99-1.74 (m, 10H), 1.64-1.59 (m, 2H). HRMS *m/z* $(M+H)^{+}$ calcd: 594.3114, obsd: 594.3114.

Example 405

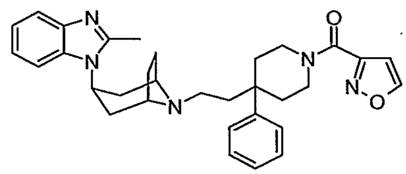
Prearation of (2S,3R)-N[1],N[1]-bis{4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-[N-(methylsulfonyl)-L-threonyl]-4-phenylpiperidin-2-yl}-N[2]-(methylsulfonyl)-L-threoninamide



(2*S*, 3*R*)-*N*[1],*N*[1]-Bis{4-{2-[(1*R*, 5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-[*N*-(methylsulfonyl)-*L*-threonyl]-4-phenylpiperidin-2-yl}-*N*[2]-(methylsulfonyl)-*L*-threoninamide (54 mg, 63%) was obtained as amorphous solid from 2-methyl-1-{8-[2-(4-phenylpiperidin-4-yl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1*H*-benzimidazole dihydrochloride (70 mg, 0.14 mmol), *N*-(methylsulfonyl)-*L*-threonine (33 mg, 0.17 mmol, prepared from *L*-threonine and methanesulfonyl chloride) and HATU (57 mg, 0.15 mmol) by the similar procedure outlined in example 5. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (d, J=8.6Hz, 1H), 7.38-7.35 (m, 2H), 7.28-7.22 (m, 4H), 7.18-7.11 (m, 2H), 6.00 (br, 1H), 4.64-4.54 (m, 1H), 4.29 (d, J=9.7Hz, 1H), 4.08-4.00 (m, 1H), 3.94-3.91 (m, 1H), 3.77-3.71 (m, 1H), 3.40-3.06 (m, 5H), 2.98 (s, 3/2H), 2.84 (s, 3/2H), 2.56 (s, 3H), 2.39-2.20 (m, 4H), 1.98-1.73 (m, 10H), 1.62-1.57 (m, 2H), 1.32 (d, J=6.2Hz, 3/2H), 1.25 (d, J=6.2Hz, 3/2H). HRMS *m/z* $(M+H)^+$ calcd: 608.3271, obsd: 608.3283.

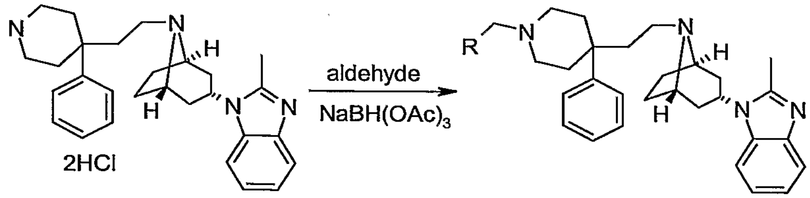
Example 406

Preparation of 1-(8-{2-[1-(isoxazol-3-ylcarbonyl)-4-phenylpiperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1H-benzimidazole



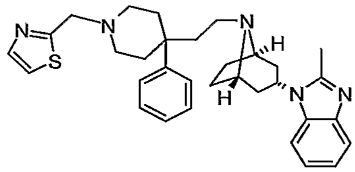
To a pre-cooled (0 °C) solution of 2-methyl-1-{8-[2-(4-phenylpiperidin-4-yl)ethyl]-8-azabicyclo [3.2.1]oct-3-yl}-1*H*-benzimidazole dihydrochloride (25.3 mg, 0.05 mmol) in dichloromethane (3 mL) was added isoxazole-5-carbonyl chloride (7.2 mg, 0.055 mmol) and triethylamine (15 μL, 0.11 mmol). The resulting mixture was stirred overnight at ambient temperature and was then diluted with ethyl acetate (20 mL). After being washed with saturated sodium bicarbonate solution, the organic phase was dried over anhydrous sodium sulfate and evaporated. The crude product was purified by flash chromatography on silical gel, eluting with a gradient of 0-10% methanol in ethyl acetate to afford 1-(8-{2-[1-(isoxazol-3-ylcarbonyl)-4-phenylpiperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1*H*-benzimidazole as amorphous solid (18.4 mg, 68%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.32 (d, J=1.8Hz), 7.67 (dd, J=2.6, 7.0Hz, 1H), 7.43-7.38 (m, 2H), 7.34-7.24 (m, 4H), 7.21-7.13 (m, 2H), 6.74 (d, J=1.8Hz), 4.64 (br, 1H), 4.23-4.18 (m, 1H), 3.93-3.89 (m, 1H), 3.45-3.27 (m, 4H), 2.58 (s, 3H), 2.44-2.31 (m, 4H), 1.96-1.86 (m, 10H), 1.67-1.60 (m, 2H). HRMS *m/z* $(M+H)^+$ calcd: 524.3026, obsd: 524.3024.

Preparation of the derivatives of 2-Methyl-1-{8-[2-(4-Phenylpiperidin-4-yl)ethyl]-8-Azabicyclo[3.2.1]oct-3-yl}-1H-benzimidazole with Heterocycle-Methylene-Piperidine Linkages by Reductive Amination



Example 407

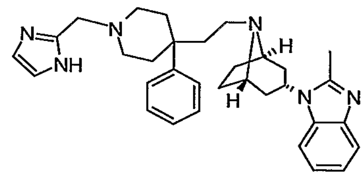
Preparation of 2-methyl-1-(8-{2-[4-phenyl-1-(1,3-thiazol-2-ylmethyl)-piperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-1H-benzimidazole



To a stirred solution of 2-methyl-1-{8-[2-(4-phenylpiperidin-4-yl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1*H*-benzimidazole dihydrochloride (25.3 mg, 0.05 mmol) in 1,2-dichloroethane (1 mL) was added triethylamine (14 μL, 0.1 mmol), 2-thiazole-carboxaldehyde (6.6 mg, 0.05 mmol) and sodium triacetoxylborohydride (10.6 mg, 0.05 mmol). The resulting mixture was stirred for 4 hours at ambient temperature before it was quenched with saturated sodium bicarbonate solution. The aqueous phase was extracted with ethyl acetate (2 x 10 mL). The combined extracts was washed with brine and dried over anhydrous sodium sulfate. After evaporation of the solvents, the residue was brought to a flash chromatography on silical gel, eluting with a gradient of 0-10% methanol in ethyl acetate to afford 2-methyl-1-(8-{2-[4-phenyl-1-(1,3-thiazol-2-ylmethyl)piperidin-4-yl]ethyl}-8-azabicyclo-[3.2.1]oct-3-yl)-1*H*-benzimidazole (23 mg, 87%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.79-7.65 (m, 2H), 7.46-7.37 (m, 2H), 7.34-7.15 (m, 7H), 5.32 (br, 1H), 3.68 (s, 2H), 3.54 (br, 2H), 2.82-2.80 (m, 2H), 2.67 (s, 3H), 2.63-2.47 (m, 4H), 2.25 (br, 4H), 2.08-1.96 (m, 8H), 1.86 (br, 2H). HRMS m/z $(M+H)^+$ calcd: 526.3004, obsd: 526.3008.

Example 408

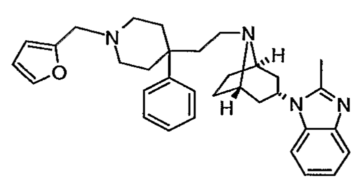
Preparation of 1-(8-{2-[1-(1H-imidazol-2-ylmethyl)-4-phenylpiperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1H-benzimidazole



1-(8-{2-[1-(1*H*-imidazol-2-ylmethyl)-4-phenylpiperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1*H*-benzimidazole (9.9 mg, 39%) was obtained as amorphous solid from 2-methyl-1-{8-[2-(4-phenylpiperidin-4-yl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1*H*-benzimidazole dihydrochloride (25.3 mg, 0.05 mmol) and imidazol-2-carboxaldehyde (14.4 mg, 0.15 mmol) following the procedure outlined in example 407. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.78 (s, 10H), 7.69 (d, J=7.1 Hz, 2H), 7.41-7.27 (m, 5H), 7.25-7.17 (m, 3H), 7.03 (s, 2H), 4.68-4.63 (m, 1H), 3.63 (s, 2H), 3.26 (br, 2H), 2.66-2.64 (m, 2H), 2.60 (s, 3H), 2.45-2.35 (m, 4H), 2.20-2.10 (m, 4H), 1.96-1.71 (m, 8H), 1,63 (d, J=7.7Hz, 2H). HRMS *m/z* $(M+H)^+$ calcd: 509.3393, obsd: 509.3393.

Example 409

Preparation of 1-(8-{2-[1-(2-furylmethyl)-4-phenylpiperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1H-benzimidazole

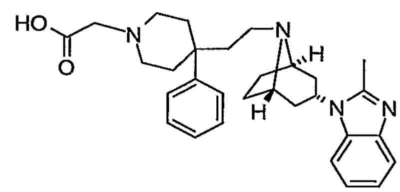


1-(8-{2-[1-(2-Furylmethyl)-4-phenylpiperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1*H*-benzimidazole (18.4 mg, 72 %) was obtained as oil from 2-methyl-1-{8-[2-(4-phenylpiperidin-4-yl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1*H*-benzimidazole dihydrochloride (25.3 mg, 0.05 mmol) and 2-furaldehyde (4.8 mg, 0.05 mmol) following the procedure outlined in example 407. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.69 (d, J=7.0Hz, 1H), 7.40-7.19 (m, 9H), 6.34 (s, 1H), 6.19 (s, 1H), 4.68-4.61 (m, 1H), 3.50 (s, 2H),

3.25 (br, 2H), 2.67 (br, 2H), 2.60 (s, 3H), 2.45-2.26 (m, 6H), 1.96-1.80 (m, 10H), 1.62 (d, J=7.8Hz, 2H). HRMS *m/z* $(M+H)^+$ calcd: 509.3280, obsd: 509.3276.

Example 410

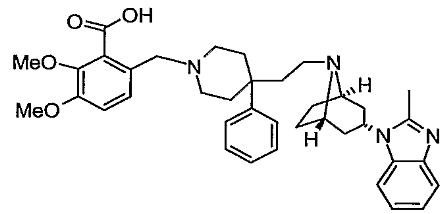
Preparation of (4-{2-[3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)acetic acid



(4-{2-[3-(2-Methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)acetic acid (5.2 mg, 21 %) was obtained as oil from 2-methyl-1-{8-[2-(4-phenylpiperidin-4-yl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1*H*-benzimidazole dihydro-chloride (25.3 mg, 0.05 mmol) and glyoxylic acid monohydrate (4.6 mg, 0.05 mmol) following the procedure outlined in example 407. ^1H NMR (300 MHz, $CDCl_3$) δ 7.69 (s, 1H), 7.44 (d, J=7.3 Hz, 2H), 7.33-7.28 (m, 4H), 7.21 (br, 2H), 4.63 (m, 1H), 3.93-3.85 (m, 3H), 3.32 (br, 2H), 3.10-3.06 (m, 2H), 2.63 (s, 3H), 2.54-2.33 (m, 4H), 2.01-1.90 (m, 11H), 1.68 (d, J=7.7Hz, 2H). HRMS *m/z* $(M+H)^+$ calcd: 487.3073, obsd: 487.3089.

Example 411

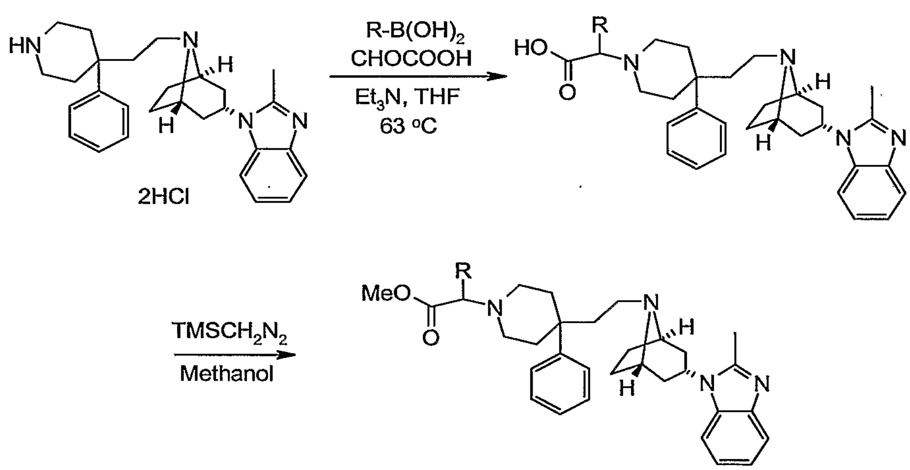
Preparation of 2,3-dimethoxy-6-[(4-{2-[3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)methyl]benzoic acid



2,3-Dimethoxy-6-[(4-{2-[3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo-[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)methyl]benzoic acid

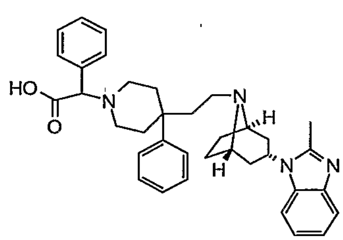
(14.4 mg, 46%)was obtained as oil from 2-methyl-1-{8-[2-(4-phenylpiperidin-4-yl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1*H*-benzimidazole dihydrochloride (25.3 mg, 0.05 mmol) and 6-formyl-2,3-dimethoxybenzoic acid (10.5 mg, 0.05 mmol) following the procedure outlined in example 407. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.69 (d, J=7.4Hz, 1H), 7.41-7.39 (m, 2H), 7.30-7.23 (m, 4H), 7.23-7.14 (m, 2H), 6.81-6.77 (m, 2H), 4.63-4.58 (m, 1H), 3.95 (s, 3H), 3.86 (s, 3H), 3.65 (s, 2H), 3.23 (br, 2H), 2.95 (br, 2H), 2.57 (s, 3H), 2.42-2.38 (m, 6H), 1.94-1.81 (m, 10H), 1.62 (d, J=7.7Hz, 2H). HRMS *m/z* $(M+H)^+$ calcd: 623.3597, obsd: 623.3585.

<u>Preparation of Substituted Phenyl Acetic Acid Derivatives of 2-Methyl-1-{8-[2-(4-Phenylpiperidin-4-yl)ethyl]-8-Azabicyclo[3.2.1]oct-3-yl}-1H-benzimidazole by Petasis Coupling</u>



Example 412

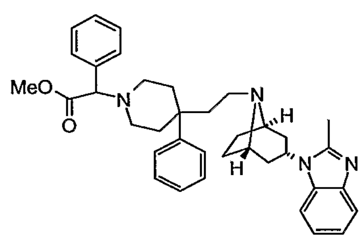
<u>Preparation of (4-{2-[3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo-[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)(phenyl)acetic acid</u>



To a stirred solution of 2-methyl-1-{8-[2-(4-phenylpiperidin-4-yl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1*H*-benzimidazole dihydrochloride (25.3 mg, 0.05 mmol) in THF (3 mL) was added triethyl amine (14 μL), glyoxylic acid monohydrate (4.6 mg, 0.05 mmol) and phenyl boronic acid (6.1 mg, 0.05 mmol). The resulting mixture was then purged with nitrogen and sealed. After being heated to 60 °C for 3 hours, the solvent was evaporated and the residue was purified by flash chromatography on silical gel, eluting with a gradient of 10-80% methanol in ethyl acetate to afford (4-{2-[3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)(phenyl)acetic acid (22 mg, 76%). ^{1}H NMR (300 MHz,DMSO-d_6) δ 9.41 (s, 1H), 7.53-7.48 (m, 3H), 7.36-7.34 (m, 8H), 7.24-7.23 (m, 1H), 7.17-7.09 (m, 2H), 4.58-4.45 (m, 1H), 4.20 (s, 1H), 3.24-3.21 (m, 2H), 3.08 (br, 1H), 2.82-2.65 (m, 2H), 2.82-2.65 (m, 2H), 2.44 (s, 3H), 2.39-2.05 (m, 7H), 1.83-1.68 (m, 8H), 1.59 (d, J=7.6Hz, 2H). HRMS *m/z* $(M+H)^+$ calcd: 563.3386, obsd: 563.3390.

Example 413

Synthesis of methyl (4-{2-[3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)(phenyl)acetate

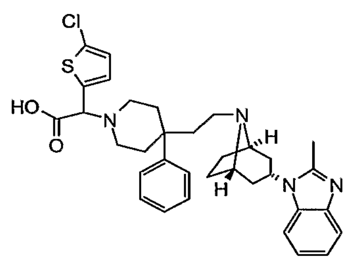


To a stirred solution of (4-{2-[3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo-[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)(phenyl)acetic acid (prepared above) (12 mg, 0.02 mmol) in methanol (2 mL) was added (tirmethylsilyl)diazomethane (100 μL, 2.0 M in hexans). The reaction mixture was stirred for 30 minutes at room temperature. After evaporation of the solvents, the residue was purified by flash chromatography, eluting with a gradient of 0-10% methanol in ethyl acetate, to afford an oil (10 mg, 81%) as

methyl (4-{2-[3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)(phenyl)acetate. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.67 (d, J=7.1Hz, 1H), 7.45-7.42 (m, 2H), 7.37-7.27 (m, 8H), 7.23-7.15 (m, 3H), 4.61 (m, 1H), 3.89 (s, 1H), 3.67 (s, 3H), 3.25-3.24 (m, 2H), 2.72-2.70 (m, 1H), 2.55 (s, 4H), 2.42-2.16 (m, 6H), 2.03-1.85 (m, 7H), 1.81-1.76 (m, 3H), 1.61-1.58 (m, 2H). HRMS *m/z* $(M+H)^+$ calcd: 577.3543, obsd: 577.3557.

Example 414

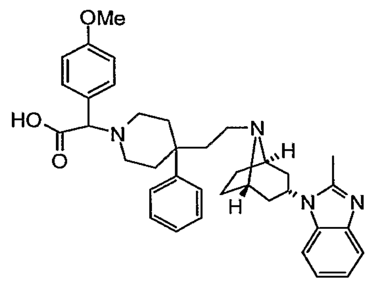
Preparation of (5-chlorothien-2-yl)(4-{2-[3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)acetic acid



(5-Chlorothien-2-yl)(4-{2-[3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)acetic acid (29 mg, 96%) was obtained as amorphous solid from 2-methyl-1-{8-[2-(4-phenylpiperidin-4-yl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1*H*-benzimidazole dihydrochloride (25.3 mg, 0.05 mmol) and 5-chlorothiophene-2-boronic acid (8.1 mg, 0.05 mmol) following the procedure outlined in example 412. ^{1}H NMR (300 MHz, DMSO-d_6, 100°C) δ 7.50-7.45 (m, 1H), 7.38-7.32 (m, 5H), 7.17-7.12 (m, 3H), 6.99-6.86 (m, 2H), 4.61-4.57 (m, 1H), 4.30-4.24 (m, 1H), 3.23 (br, 3H), 2.82-2.80 (m, 3H), 2.57-2.37 (m, 7H), 2.14 (br, 2H), 1.93-1.77 (m, 8H), 1.64-1.61 (m, 2H). HRMS *m/z* $(M+H)^+$ calcd: 603.2561, obsd: 603.2552.

Example 415

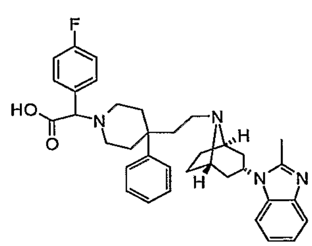
Preparation of (4-methoxyphenyl)(4-{2-[3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)acetic acid



(4-Methoxyphenyl)(4-{2-[3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)acetic acid (25.6 mg, 86%) was obtained as amorphous solid from 2-methyl-1-{8-[2-(4-phenylpiperidin-4-yl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1*H*-benzimidazole dihydrochloride (25.3 mg, 0.05 mmol) and 4-methoxyphenylboronic acid (7.6 mg, 0.05 mmol) following the procedure outlined in example 412. ^{1}H NMR (300 MHz, DMSO-d$_6$, 80°C) δ 9.44 (s, 1H), 7.52 (d, J=7.0Hz, 1H), 7.38-7.36 (m, 7H), 7.24-7.21 (m, 1H), 7.17-7.12 (m, 2H), 6.92 (d, J=8.2Hz, 2H), 4.60-4.51 (m, 1H), 4.04 (s, 1H), 3.78 (s, 3H), 3.26-3.22 (m, 3H), 2.97-2.90 (m, 2H), 2.75 (br, 1H), 2.47 (s, 3H), 2.40-1.81 (m, 9H), 1.63 (d, J=7.3Hz, 2H). HRMS *m/z* $(M+H)^+$ calcd: 593.3492, obsd: 593.3496.

Example 416

Preparation of (4-fluorophenyl)(4-{2-[3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)acetic acid

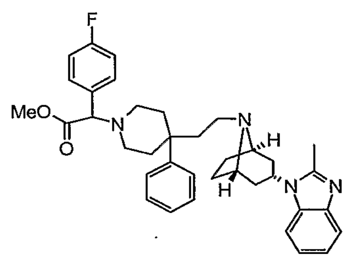


(4-Fluorophenyl)(4-{2-[3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)acetic acid (24.5 mg, 84%) was obtained as amorphous solid from 2-methyl-1-{8-[2-(4-

phenylpiperidin-4-yl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1*H*-benzimidazole dihydrochloride (25.3 mg, 0.05 mmol) and 4-fluorophenylboronic acid (7 mg, 0.05 mmol) following the procedure outlined in example 412. ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.52-7.48 (m, 3H), 7.37-7.35 (m, 4H), 7.24-7.05 (m, 6H), 4.54-4.48 (m, 1H), 4.07 (s, 1H), 3.23 (br, 2H), 2.98 (br, 1H), 2.69-2.63 (m, 2H), 2.45 (s, 3H), 2.42-2.31 (m, 3H), 2.18 (br, 2H), 2.00 (br, 2H), 1.87-1.74 (m, 8H), 1,59 (d, J=7.3Hz, 2H). HRMS *m/z* $(M+H)^+$ calcd: 581.3293, obsd: 581.3287.

Example 417

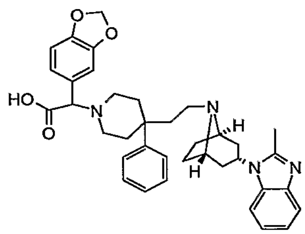
Synthesis of methyl (4-fluorophenyl)(4-{2-[3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)acetate



Methyl (4-fluorophenyl)(4-{2-[3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)acetate (12 mg, 96%) was obtained as a solid from (4-fluorophenyl)(4-{2-[3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)acetic acid (12 mg, 0.02 mmol) and (trimethylsilyl)diazomethane (100 μL 2.0 M in hexanes) following the procedure outlined for example 9. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.67 (d, J=7.1Hz, 1H), 7.47-7.45 (m, 1H), 7.41-7.38 (m, 2H), 7.32-7.29 (m, 5H), 7.17-7.11 (m, 3H), 7.09-7.06 (m, 2H), 4.60-4.40 (m, 1H), 4.00 (s, 1H), 3.54 (s, 3H), 3.17 (br, 2H), 2.60-2.43 (m, 1H), 2.43-2.41 (m, 4H), 2.33-2.25 (m, 2H), 2.24-2.20 (m, 1H), 2.19-2.00 (m, 3H), 1.78-1.69 (m, 10H), 1.54 (d, J=7.5Hz, 2H). HRMS *m/z* $(M+H)^+$ calcd: 595.3448, obsd: 595.3467.

Example 418

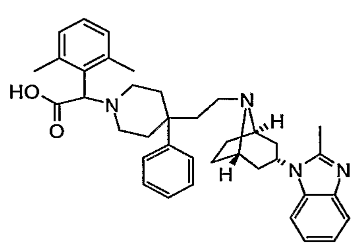
Preparation of 1,3-benzodioxol-5-yl(4-{2-[3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)acetic acid



1,3-Benzodioxol-5-yl(4-{2-[3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)acetic acid (25 mg, 81%) was obtained as amorphous solid from 2-methyl-1-{8-[2-(4-phenylpiperidin-4-yl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1H-benzimidazole dihydrochloride (25.3 mg, 0.05 mmol) and 3,4-dioxolmethylenephenyl boronic acid (9.3 mg, 0.05 mmol) following the procedure outlined in example 412. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.40 (s, 1H), 7.52 (m, 1H), 7.38-7.37 (m, 5H), 7.24 (m, 1H), 7.17-7.08 (m, 3H), 6.96-6.87 (m, 2H), 6.03 (d, J=5.1Hz, 2H), 4.45-4.48 (m, 1H), 4.16 (s, 1H), 3.23-3.08 (m, 5H), 2.82 (br, 2H), 2.45 (s, 3H), 2.40-2.01 (m, 6H), 1.82-1.79 (m, 7H), 1.60 (d, J=7.4Hz, 2H). HRMS *m/z* $(M+H)^+$ calcd: 607.3284, obsd: 607.3270.

Example 419

Preparation of (2,6-dimethylphenyl)(4-{2-[3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)acetic acid

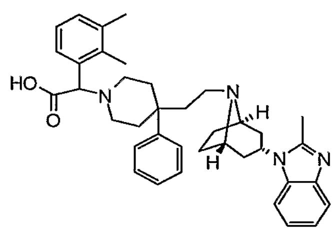


(2,6-Dimethylphenyl)(4-{2-[3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)acetic acid (26 mg, 90%) was obtained as amorphous solid from 2-methyl-1-{8-[2-(4-phenylpiperidin-4-yl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1*H*-benzimidazole

dihydrochloride (25.3 mg, 0.05 mmol) and 2,6-dimethylphenyl boronic acid (9 mg, 0.06 mmol) following the procedure outlined in example 412. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.31 (s, 1H), 7.48 (d, J=6.9Hz, 1H), 7.33-7.32 (m, 5H), 7.19-7.17 (m, 1H), 7.13-6.96 (m, 5H), 4.5-4.49 (m, 1H), 4.29 (s, 1H), 3.24 (br, 2H), 2.83 (br, 1H), 2.41 (s, 3H), 2.37 (m, 7H), 2.29-2.07 (m, 5H), 1.97-1.72 (m, 10H), 1.58 (d, J=7.2Hz, 2H). HRMS *m/z* $(M+H)^+$ calcd: 591.3699, obsd: 591.3690.

Example 420

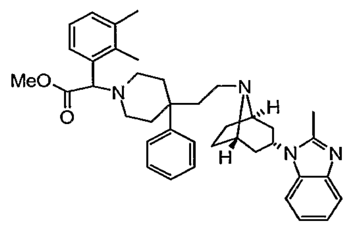
Preparation of (2,3-dimethylphenyl)(4-{2-[3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)acetic acid



(2,3-Dimethylphenyl)(4-{2-[3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)acetic acid (35 mg, 99%) was obtained as amorphous solid from 2-methyl-1-{8-[2-(4-phenylpiperidin-4-yl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1*H*-benzimidazole dihydrochloride (30 mg, 0.06 mmol) and 2,3-dimethylphenyl boronic acid (10.5 mg, 0.07 mmol) following the procedure outlined in example 412. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.37 (s, 1H), 7.49-7.47 (m, 1H), 7.39-7.32 (m, 6H), 7.22-7.18 (m, 1H), 7.13-7.03 (m, 4H), 4.5-4.44 (m, 2H), 3.23 (br, 2H), 3.04-2.88 (m, 2H), 2.71 (br, 1H), 2.56-2.51 (m, 1H), 2.39 (s, 3H), 2.36-2.29 (m, 2H), 2.25 (s, 3H), 2.22 (s, 3H), 2.15-1.93 (m, 5H), 1.81 (br, 7H), 1.58 (d, J=7.2Hz, 2H). HRMS *m/z* $(M+H)^+$ calcd: 591.3699, obsd: 591.3706.

Example 421

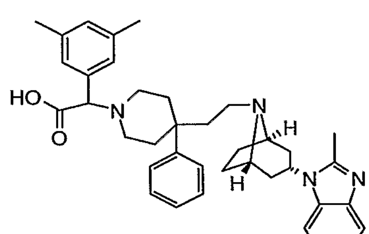
Synthesis of methyl (2,3-dimethylphenyl)(4-{2-[3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)acetate



Methyl (2,3-dimethylphenyl)(4-{2-[3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)acetate (40 mg, 66%) was obtained as a solid from (2,3-Dimethylphenyl)(4-{2-[3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1] oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)acetic acid (40 mg, 0.067 mmol) and (trimethylsilyl)diazomethane (300 μL 2.0 M in hexanes) following the procedure outlined for example 9. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.67 (d, J=7.8Hz, 1H), 7.44-7.27 (m, 6H), 7.23-7.15 (m, 3H), 7.10-7.07 (m, 2H), 4.66-4.59 (m, 1H), 4.30 (s, 1H), 3.65 (s, 3H), 3.25 (br, 2H), 2.77 (br, 1H), 2.67 (br, 1H), 2.56 (s, 3H), 2.47-2.32 (m, 3H), 2.29 (s, 6H), 2.26-2.12 (m, 3H), 1.99-183 (m, 10H), 1.61-1.59 (m, 2H). HRMS *m/z* $(M+H)^+$ calcd: 605.3856, obsd: 605.3863.

Example 422

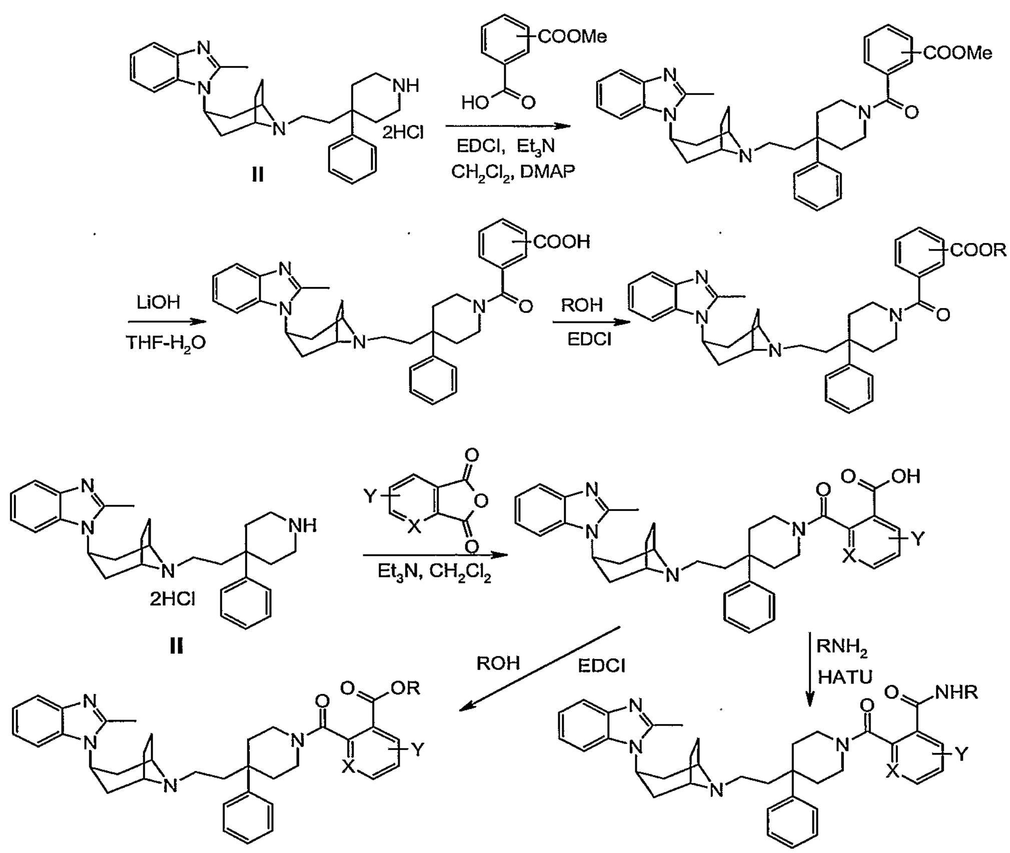
Preparation of (3,5-dimethylphenyl)(4-{2-[3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)acetic acid



3,5-Dimethylphenyl)(4-{2-[3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl) acetic acid (28 mg, 94%) was obtained as amorphous solid from 2-methyl-1-{8-[2-(4-phenylpiperidin-4-yl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1*H*-benzimidazole

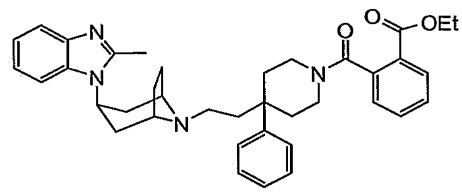
dihydrochloride (25 mg, 0.05 mmol) and 3,5-dimethylphenyl boronic acid (9.0 mg, 0.06 mmol) following the procedure outlined in example 412. ^{1}H NMR (300 MHz, DMSO-d$_6$) δ 9.37 (s, 1H), 7.48-7.47 (m, 1H), 7.35-7.33 (m, 5H), 7.23-7.19 (m, 1H), 7.11-7.07 (m, 4H), 6.94 (s, 1H), 4.53-4.47 (m, 1H), 4.13 (s, 1H), 3.23-3.15 (m, 4H), 2.83 (br, 2H), 2.39 (s, 3H), 2.36-2.25 (m, 3H), 2.21 (s, 6H), 2.14 (m, 4H), 1.81-1.70 (m, 8H), 1.58 (d, J=7.6Hz, 2H). HRMS *m/z* $(M+H)^+$ calcd: 591.3699, obsd: 591.3707.

<u>Preparation of ortho-, meta- and para-Carboxyl Benezamide Derivatives of 2-Methyl-1-{8-[2-(4-Phenylpiperidin-4-yl)ethyl]-8-Azabicyclo[3.2.1]oct-3-yl}-1H-Benzimidazole</u>



Example 423

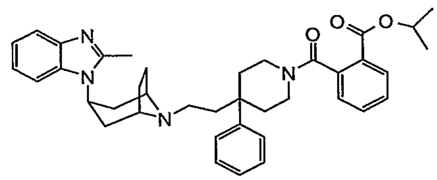
Preparation of ethyl 2-[(4-{2-[3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]benzoate



To a stirred solution of 2-[(4-{2-[3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo-[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]benzoic acid (58 mg, 0.1 mmol) in dichloromethane (5 mL) was added ethanol (8.6 μL, 0.1 mmol) and triethyl amine (13 μL, 0.1 mmol). The resulting mixture was then cooled down on an ice-water bath before the addition of 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (19 mg, 0.1 mmol) and 4-dimethylamino-pyridine (catalytic amount). After being stirred overnight at ambient temperature, the reaction mixture was diluted with dichloromethane (40 mL) and washed with saturated sodium bicarbonate solution. The organic phase was dried over anhydrous sodium sulfate. After evaporation of the solvent, the crude product was purified by flash chromatography on silical gel, eluting with a gradient of 0-10% methanol in ethyl acetate to afford methyl 4-[(4-{2-[3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]benzoate as amorphous solid (29 mg, 50%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.01 (d, J=7.9Hz, 1H), 7.64 (d, J=7.6Hz, 1H), 7.53 (br, 1H), 7.42 (t, J=7.6Hz, 1H), 7.37-7.33 (m, 2H), 7.28-7.20 (m, 4H), 7.17-7.10 (m, 3H), 4.61-4.53 (m, 1H), 4.25 (br, 3H), 3.26-3.19 (m, 4H), 3.08 (br, 1H), 2.52 (s, 3H), 2.39-2.30 (m, 3H), 1.98-1.76 (m, 11H), 1.59 (d, J=7.8Hz, 2H), 1.37-1.18 (br, 3H). HRMS *m/z* $(M+H)^+$ calcd: 605.3491, obsd: 605.3496.

Example 424

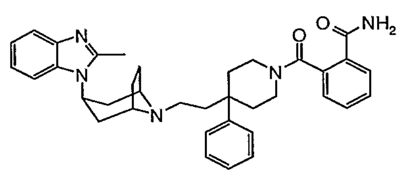
Preparation of isopropyl 2-[(4-{2-[3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]benzoate



Isopropyl 2-[(4-{2-[3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]benzoate (12 mg, 19%) was obtained as an oil from 2-[(4-{2-[3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo-[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]benzoic acid (58 mg, 0.1 mmol), isopropyl alcohol (10 μL, 0.15 mmol) and 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (19 mg, 0.1 mmol) followed the procedure outlined in example 423. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (d, J=7.7Hz, 1H), 7.64 (d, J=7.7Hz, 1H), 7.52 (br, 1H), 7.42 (t, J=7.6Hz, 1H), 7.37-7.33 (m, 2H), 7.28-7.20 (m, 4H), 7.18-7.10 (m, 3H), 5.22-5.08 (m, 1H), 4.63-4.53 (m, 1H), 4.34-3.67 (m, 2H), 3.26-3.00 (m, 4H), 2.53 (s, 3H), 2.48-2.30 (m, 2H), 2.17-2.07 (br, 2H), 1.96-1.62 (m, 10H), 1.59 (d, J=7.3Hz, 2H), 1.35-1.09 (m, 6H). HRMS *m/z* $(M+H)^+$ calcd: 619.3648, obsd: 619.3637.

Example 425

Preparation of 2-[(4-{2-[3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]benzamide

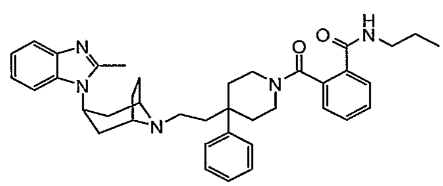


To a stirred solution of 2-[(4-{2-[3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo-[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]benzoic acid (69 mg, 0.12 mmol) in methylene chloride (4 mL) was added ammonia (1 mL, 0.5 M in dioxane), triethylamine (18 μL, 0.12 mmol) and HATU (46 mg, 0.12

mmol). The reaction mixture was stirred for 3 hours at ambient temperature before being diluted with methylene chloride and quenched with saturated sodium bicarbonate solution. The organic phase was dried over anhydrous sodium sulfate. After evaporation of the solvent, the crude product was purified by flash chromatography on silical gel, eluting with a gradient of 0-20% methanol in ethyl acetate to afford 2-[(4-{2-[3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]benzamide (57 mg, 83%) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (d, J=8.6Hz, 1H), 7.56 (d, J=7.3Hz, 1H), 7.46-7.42 (m, 2H), 7.38-7.34 (m, 2H), 7.30-7.21 (m, 4H), 7.18-7.08 (m, 3H), 6.91 (br, 1H), 5.74 (br, 1H), 4.63-4.54 (m, 1H), 4.26 (br, 1H), 3.47-3.08 (m, 5H), 2.54 (s, 3H), 2.40-2.30 (m, 3H), 2.11-2.06 (m, 1H), 1.97-1.80 (m, 10H), 1.59 (d, J=7.9Hz, 2H). HRMS *m/z* $(M+H)^+$ calcd: 576.3338, obsd: 576.3337.

Example 426

Preparation of 2-[(4-{2-[3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]-N-propylbenzamide

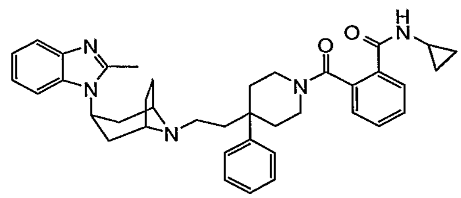


2-[(4-{2-[3-(2-Methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]-*N*-propylbenzamide (74 mg, quant.) was obtained as an oil from 2-[(4-{2-[3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo-[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]benzoic acid (69 mg, 0.12 mmol), propylamine (14 mg, 0.24 mmol) and HATU (46 mg, 0.12 mmol) following the procedure outlined in example 425. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76-7.74 (m, 1H), 7.65 (d, J=7.3Hz, 1H), 7.43 (br, 2H), 7.37-7.34 (m, 2H), 7.30-7.23 (m, 4H), 7.18-7.11 (m, 3H), 6.88-6.73 (br, 1H), 4.63-4.54 (m, 1H), 4.19 (br, 1H), 3.36-3.06 (m, 7H), 2.54 (s, 3H), 2.40-2.29 (m, 3H),

2.11-2.08 (m, 1H), 1.97-1.79 (m, 9H), 1.72-1.53 (m, 5H), 1.25-0.83 (m, 3H). HRMS *m/z* $(M+H)^+$ calcd: 618.3808, obsd: 618.3811.

Example 427

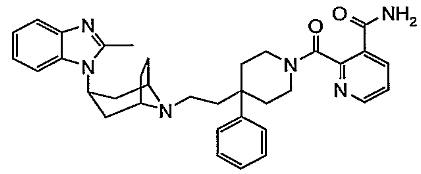
Preparation of N-cyclopropyl-2-[(4-{2-[3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]benzamide



N-Cyclopropyl-2-[(4-{2-[3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]benzamide (61 mg, 83%) was obtained as an oil from 2-[(4-{2-[3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo-[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]benzoic acid (69 mg, 0.12 mmol), cyclopropylamine (14 mg, 0.24 mmol) and HATU (46 mg, 0.12 mmol) following the procedure outlined in example 425. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (d, J=7.9Hz, 1H), 7.65 (d, J=7.3Hz), 7.41-7.33 (m, 4H), 7.29-7.23 (m, 4H), 7.21-7.09 (m, 3H), 7.03-6.84 (m, 1H), 4.63-4.54 (m, 1H), 4.20-4.17 (m, 1H), 3.37-3.22 (m, 4H), 3.10-3.05 (m, 1H), 2.92-2.70 (m, 1H), 2.54 (s, 3H), 2.36-2.29 (m, 3H), 2.11 (br, 1H), 1.98-1.61 (m, 10H), 1.59 (d, J=7.9Hz, 2H), 0.86-0.47 (m, 4H). HRMS *m/z* $(M+H)^+$ calcd: 616.3651, obsd: 616.3649.

Example 428

Preparation of 2-[(4-{2-[3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]nicotinamide

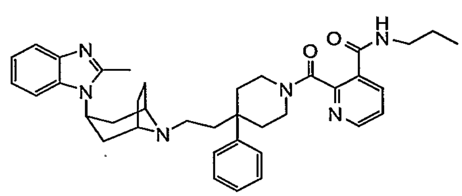


To a stirred solution of 2-methyl-1-{8-[2-(4-phenylpiperidin-4-yl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1*H*-benzimidazole (51 mg, 0.12 mmol) in dichloro-

methane (4 mL) was added 2.3-pyridinedicarboxylic anhydride (18 mg, 0.12 mmol) and triethylamine (17 μL, 0.12 mmol). The resulting mixture was stirred for 2 hours at ambient temperature before addition of ammonia (1 mL, 0.5 M in doxane) and 47 mg of HATU. The reaction mixture was then stirred for another 2 hours. After being diluted with methylene chloride and washed with saturated sodium bicarbonate solution, the organic phase was dried over anhydrous sodium sulfate. Evaporation of the solvent and purification by flash chromatography afforded 2-[(4-{2-[3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]nicotinamide as a foam (51 mg, 69%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.63-8.61 (m, 1H), 8.17 (d, J=6.8Hz, 1H), 7.66-7.64 (m, 2H), 7.38-7.33 (m, 3H), 7.30-7.22 (m, 4H), 7.20-7.10 (m, 2H), 5.79 (s, 1H), 4.61-4.55 (m, 1H), 4.27-4.22 (m, 1H), 3.40-3.08 (m, 5H), 2.54 (s, 3H), 2.47-2.33 (m, 3H), 2.19-2.15 (m, 1H), 1.97-1.80 (m, 10H), 1.63-1.61 (m, 2H). HRMS *m/z* $(M+H)^+$ calcd: 577.3291, obsd: 577.3286.

Example 429

Preparation of 2-[(4-{2-[3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]-N-propylnicotinamide

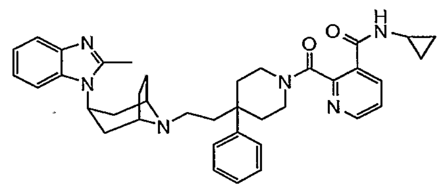


2-[(4-{2-[3-(2-Methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]-*N*-propylnicotinamide (68 mg, 99%) was obtained as a foam from 2-methyl-1-{8-[2-(4-phenylpiperidin-4-yl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1*H*-benzimidazole (51 mg, 0.12 mmol), 2.3-pyridinedicarboxylic anhydride (18 mg, 0.12 mmol), propylamine (14 mg, 0.24 mmol) and HATU (47 mg, 0.12 mmol), following the procedure outlined in example 428. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.62-8.60 (m, 1H), 8.16 (d, J=7.9Hz, 1H), 7.65 (d, J=8.6Hz, 1H), 7.57 (t, J=5.7Hz, 1H), 7.39-7.33 (m, 3H),

7.30-7.21 (m, 4H), 7.18-7.11 (m, 2H), 4.61-4.56 (m, 1H), 4.27-4.22 (dt, J=13.2, 4.3Hz, 1H), 3.38-3.31 (m, 3H), 3.22-3.06 (m, 4H), 2.54 (s, 3H), 2.40-2.31 (m, 3H), 2.17-2.14 (m, 1H), 1.92-1.80 (m, 10H), 1.62-1.52 (m, 4H), 0.93 (t, J=7.3Hz, 3H). HRMS *m/z* $(M+H)^+$ calcd: 619.3761, obsd: 619.3785.

Example 430

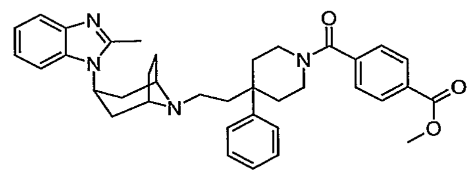
Preparation of N-cyclopropyl-2-[(4-{2-[3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]nicotinamide



N-Cyclopropyl-2-[(4-{2-[3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]nicotinamide (58 mg, 78%) was obtained as a foam from 2-methyl-1-{8-[2-(4-phenylpiperidin-4-yl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1*H*-benzimidazole (51 mg, 0.12 mmol), 2.3-pyridinedicarboxylic anhydride (18 mg, 0.12 mmol), cyclopropylamine (14 mg, 0.24 mmol) and HATU (47 mg, 0.12 mmol) following the procedure outlined in example 428. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.56-8.54 (m, 1H), 8.03 (d, J=7.8Hz, 1H), 7.80 (s, 1H), 7.65 (d, J=7.0Hz, 1H), 7.37-7.22 (m, 5H), 7.20-7.12 (m, 2H), 4.62-4.55 (m, 1H), 4.23-4.19 (m, 1H), 3.35 (t, J=10.6Hz, 1H), 3.22-3.06 (m, 4H), 2.89-2.87 (m, 1H), 2.54 (s, 3H), 2.47-2.33 (m, 3H), 2.18-2.09 (m, 1H), 1.88-1.83 (m, 10H), 1.61-1.58 (m, 2H), 0.84-0.62 (m, 2H), 0.59-0.56 (m, 2H). HRMS *m/z* $(M+H)^+$ calcd: 617.3604, obsd: 617.3627.

Example 431

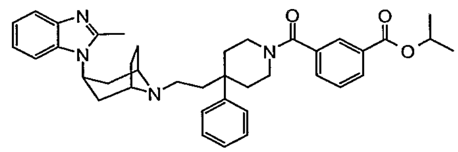
Preparation of methyl 4-[(4-{2-[3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]benzoate



To a stirred solution of 2-methyl-1-{8-[2-(4-phenylpiperidin-4-yl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1*H*-benzimidazole dihydrochloride (50.5 mg, 0.1 mmol) in dichloromethane (5 mL) was added terephthalic acid monomethyl ester (18 mg, 0.1 mmol) and triethyl amine (30 µL, 0.2 mmol). The resulting mixture was then cooled down on an ice-water bath before the addition of 1-[3-(dimethylamino)propyl]-3-ethylcarbo-diimide hydrochloride (19 mg, 0.1 mmol) and 4-dimethylaminopyridine (catalytic amount). After being stirred overnight at ambient temperature, the reaction mixture was diluted with dichloromethane (40 mL) and washed with saturated sodium bicarbonate solution. The organic phase was dried over anhydrous sodium sulfate. After evaporation of the solvent, the crude product was purified by flash chromatography on silical gel, eluting with a gradient of 0-10% methanol in ethyl acetate to afford methyl 4-[(4-{2-[3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]benzoate as amorphous solid (65 mg, quant.). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.11 (d, J=8.2Hz, 2H), 7.69 (d, J=7.2Hz, 1H), 7.47 (d, J=8.2Hz, 2H), 7.41 (d, J=7.3Hz, 2H), 7.34-7.24 (m, 4H), 7.21-7.15 (m, 2H), 4.66 (br, 1H), 4.26-4.21 (m, 1H), 3.97 (s, 3H), 3.52-3.30 (m, 5H), 2.60 (s, 3H), 2.40 (br, 3H), 2.21-2.17 (br, 1H), 1.99-1.79 (m, 10H), 1.68-1.66 (m, 2H). HRMS *m/z* $(M+H)^+$ calcd: 591.3335, obsd: 591.3320.

Example 432

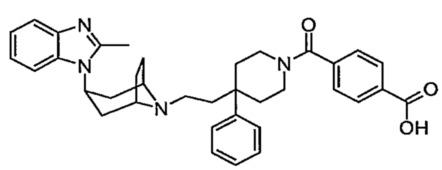
Preparation of isopropyl 3-[(4-{2-[3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]benzoate



Isopropyl 3-[(4-{2-[3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]benzoate (10 mg, 16%) was obtained as an oil from 3-[(4-{2-[3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo-[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]benzoic acid (70 mg, 0.12 mmol), isopropyl alcohol (10 μL, 0.12 mmol) and 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (23 mg, 0.12 mmol) following the procedure outlined in example 423. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (d, J=7.9Hz, 1H), 8.04 (s, 1H), 7.64 (d, J=7.2Hz, 1H), 7.54 (d, J=7.7Hz, 1H), 7.46 (t, J=7.7Hz, 1H), 7.39-7.35 (m, 1H), 7.29-7.26 (m, 4H), 7.18-7.11 (m, 3H), 5.25-5.22 (m, 1H), 4.59 (br, 1H), 4.20 (br, 1H), 3.52 (br, 1H), 3.35 (br, 1H), 3.24 (br, 3H), 2.54 (s, 3H), 2.37-2.32 (m, 3H), 2.16 (br, 1H), 1.92-1.75 (m, 10H), 1.60 (d, J=7.7Hz, 2H), 1.35 (d, J=6.2Hz, 6H). HRMS *m/z* $(M+H)^+$ calcd: 619.3648, obsd: 619.3649.

Example 433

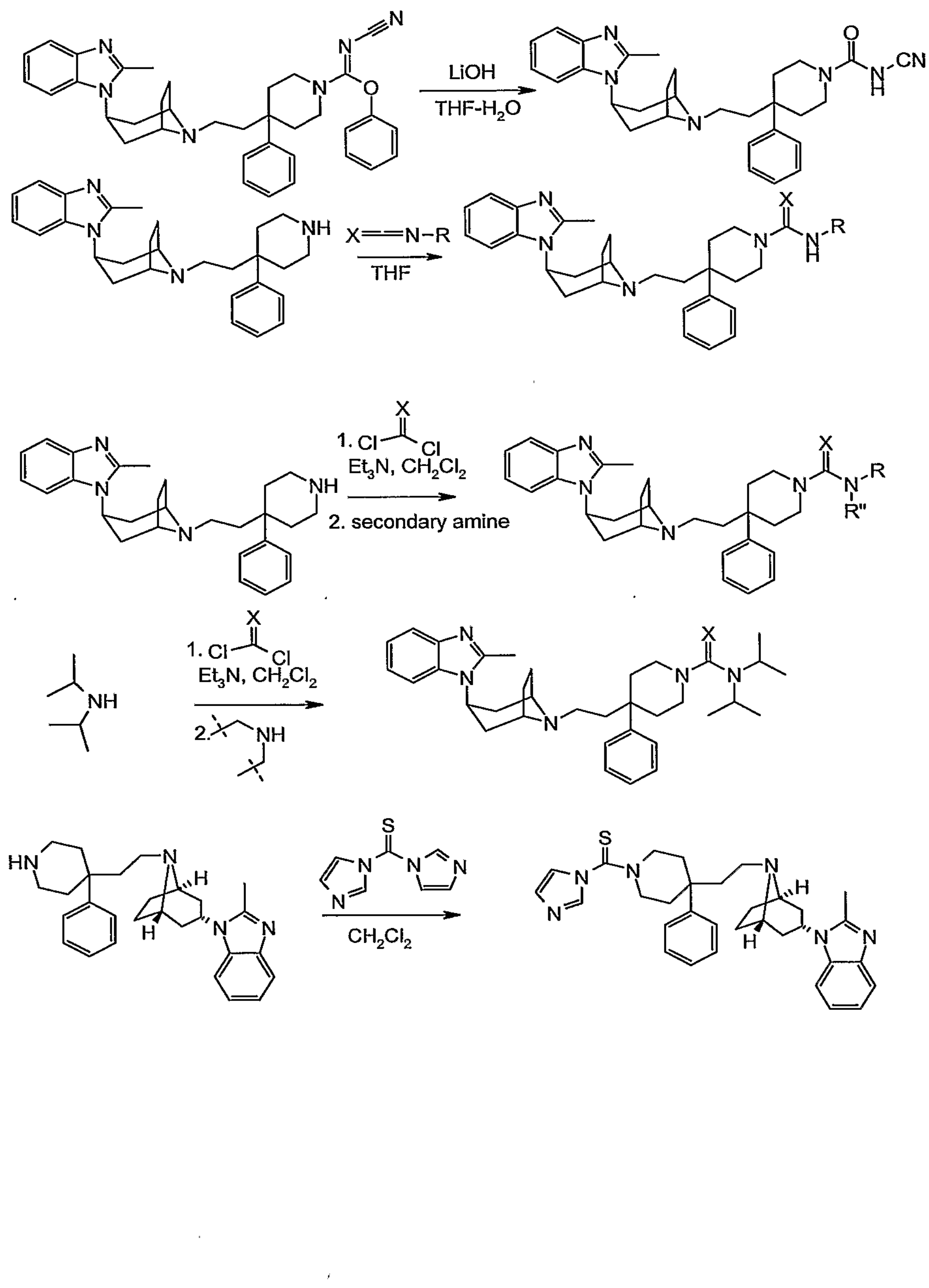
Preparation of 4-[(4-{2-[3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo-[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]benzoic acid



4-[(4-{2-[3-(2-Methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]benzoic acid (15 mg, 43 %) was obtained as white powder from methyl 4-[(4-{2-[3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-

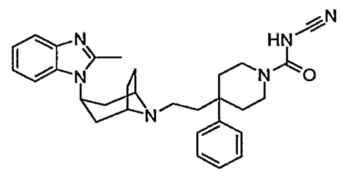
yl)carbonyl]benzoate following the procedure outlined in the previous example. HRMS m/z $(M+H)^+$ calcd: 577.3179, obsd: 577.3189.

<u>Preparation of Carboxamides and Carboxthioamides of 2-Methyl-1-{8-[2-(4-Phenylpiperidin-4-yl)ethyl]-8-Azabicyclo[3.2.1]oct-3-yl}-1H-Benzimidazole</u>



Example 434

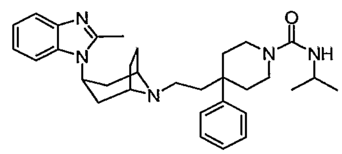
Preparation of N-cyano-4-{2-[3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidine-1-carboxamide



To a precooled (0 °C) solution of phenyl *N*-cyano-4-{2-[3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidine-1-carboximidoate (27 mg, 0.047mmol) in a mixed solvent of THF-H_2O (2 mL, 3:1) was added lithium hydroxide monhydrate (7.7 mg, 0.18 mmol). After stirring for 3 hours on an ice-water bath, the reaction mixture was diluted with dichloromethane (20 mL) and buffered with saturated sodium bicarbonate solution (10 mL). The aqueous phase was extracted with dichloromethane (3x 10 mL). The combined extracts were washed with brine and dried over anhydrous sodium sulfate. After evaporation of solvents, the residue was purified by flash chromatography on silical gel, eluting with a gradient of 10-30% methanol in ethyl acetate to afford *N*-cyano-4-{2-[3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidine-1-carboxamide as a white solid (20 mg, 83%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.46 (d, J=7.1Hz, 1H), 7.33-7.29 (m, 5H), 7.17-7.14 (m, 1H), 7.11-7.04 (m, 2H), 4.53-4.48 (m, 1H), 4.09 (br, 1H), 3.55-3.51 (m, 2H), 3.21 (br, 2H), 3.06-3.03 (m, 2H), 2.45 (s, 3H), 2.37-2.29 (m, 2H), 1.87-1.64 (m, 10H), 1.59-1.55 (m, 4H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 165.0, 152.3, 146.7, 143.7, 134.0, 128.9, 127.3, 126.2, 125.0, 121.8, 121.4, 119.4, 111.6, 57.2, 55.6, 49.3, 48.0, 46.3, 36.3, 35.9, 30.0, 21.8, 14.9. HRMS *m/z* $(M+H)^+$ calcd: 497.3029, obsd: 497.3026.

Example 435

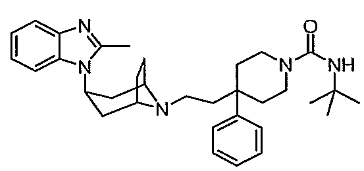
Preparation of N-isopropyl-4-{2-[3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo [3.2.1]oct-8-yl]ethyl}-4-phenylpiperidine-1-carboxamide



To a stirred solution of 2-methyl-1-{8-[2-(4-phenylpiperidin-4-yl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1*H*-benzimidazole (20 mg, 0.047 mmol) in THF (2 mL) was added isopropyl isocyanate (4.3 mg, 0.047 mmol). The resulting mixture was stirred at ambient temperature overnight. After evaporation of the solvent, the residue was purified on silical gel, eluting with a gradient of 10-30% methanol in ethyl acetate to afford *N*-isopropyl-4-{2-[3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidine-1-carboxamide as white solid (15 mg, 63%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70 (d, J=7.2Hz, 1H), 7.43-7.38 (m, 2H), 7.34-7.24 (m, 4H), 7.22-7.15 (m, 2H), 4.67 (br, 1H), 4.24 (d, J=7.3Hz, 1H), 3.99 (m, 1H), 3.62-3.58 (m, 2H), 3.30 (br, 2H), 3.23-3.16 (m, 2H), 2.62 (s, 3H), 2.42 (br, 2H), 2.25-2.20 (m, 2H), 1.98-1.83 (m, 9H), 1.68 (br, 2H), 1.17 (d, J=6.4Hz, 6H). HRMS *m/z* $(M+H)^+$ calcd: 514.3546, obsd: 514.3530.

Example 436

Preparation of N-(tert-butyl)-4-{2-[3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo [3.2.1]oct-8-yl]ethyl}-4-phenylpiperidine-1-carboxamide

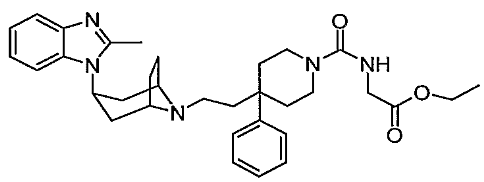


N-(*tert*-Butyl)-4-{2-[3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo-[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidine-1-carboxamide (39 mg, quant.) was obtained as syrup from 2-methyl-1-{8-[2-(4-phenyl piperidin-4-yl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1*H*-benzimidazole (30 mg, 0.07 mmol) and *t*-butyl isocyanate (6.9 mg, 0.07 mmol) following the procedure outlined in example

435. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.68 (d, J=7.5Hz, 1H), 7.41-7.36 (m, 2H), 7.32-7.22 (m, 4H), 7.20-7.13 (m, 2H), 4.75 (br, 1H), 4.31 (s, 1H), 3.57-3.53 (m, 2H), 3.35 (br, 2H), 3.18-3.12 (m, 2H), 2.62 (s, 3H), 2.47 (br, 2H), 2.22-2.17 (m, 2H), 1.97-1.81 (m, 10H), 1.71 (br, 2H), 1.34 (s, 9H). HRMS *m/z* $(M+H)^+$ calcd: 528.3702, obsd: 528.3722.

Example 437

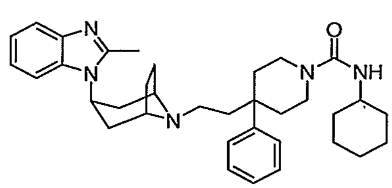
Preparation of ethyl N-[(4-{2-[3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo [3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]glycinate



Ethyl *N*-[(4-{2-[3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenyl piperidin-1-yl)carbonyl]glycinate (25 mg, 64%) was obtained as an oil from 2-methyl-1-{8-[2-(4-phenyl piperidin-4-yl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1*H*-benzimidazole (30 mg, 0.07 mmol) and ethyl isocyanatoacetate (9 mg, 0.07 mmol) following the procedure outlined in example 435. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.46 (d, J=7.2Hz, 1H), 7.37-7.32 (m, 5H), 7.20-7.17 (m, 1H), 7.11-7.04 (m, 2H), 6.88 (t, J=5.6Hz, 1H), 4.51-4.47 (m, 1H), 4.02 (q, J=7.1Hz, 2H), 3.66 (d, J=5.7Hz, 2H), 3.51-3.47 (m, 2H), 3.20 (br, 2H), 3.05 (t, J=9.7Hz, 2H), 2.46 (s, 3H), 2.36-2.29 (m, 2H), 1.99 (br, 2H), 1.84-1.70 (m, 10H), 1.55 (d, J=7.5Hz, 2H), 1.13 (t, J=7.2Hz, 3H). HRMS *m/z* $(M+H)^+$ calcd: 558.3444, obsd: 558.3445.

Example 438

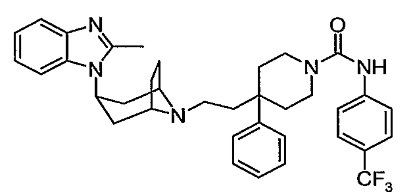
Preparation of N-cyclohexyl-4-{2-[3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo [3.2.1]oct-8-yl]ethyl}-4-phenylpiperidine-1-carboxamide



N-Cyclohexyl-4-{2-[3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidine-1-carboxamide (34 mg, 88%) was obtained as an oil from 2-methyl-1-{8-[2-(4-phenylpiperidin-4-yl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1*H*-benzimidazole (30 mg, 0.07 mmol) and cyclohexyl isocyanate (8.8 mg, 0.07 mmol) following the procedure outlined in example 435. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.46 (d, J=7.1Hz, 1H), 7.34-7.30 (m, 5H), 7.19-7.16 (m, 1H), 7.11-7.04 (m, 2H), 6.03 (d, J=7.7Hz, 1H), 4.51-4.46 (m, 1H), 3.47-3.43 (m, 2H), 3.35-3.34 (m, 1H), 3.19 (br, 2H), 3.04-2.99 (m, 2H), 2.45 (s, 3H), 2.36-2.28 (m, 2H), 2.00-1.95 (m, 2H), 1.81-1.67 (m, 14H), 1.61-1.51 (m, 3H), 1.19-1.00 (m, 5H). HRMS *m/z* $(M+H)^+$ calcd: 554.3859, obsd: 554.3863.

<u>Example 439</u>

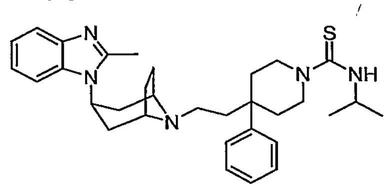
<u>Preparation of 4-{2-[3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenyl-N-[4-(trifluoromethyl)phenyl]piperidine-1-carboxamide</u>



4-{2-[3-(2-Methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenyl-*N*-[4-(trifluoromethyl)phenyl]piperidine-1-carboxamide (27 mg, 88%) was obtained as an oil from 2-methyl-1-{8-[2-(4-phenylpiperidin-4-yl)ethyl]-8-azabicyclo[3.2.1]-oct-3-yl}-1*H*-benzimidazole (22 mg, 0.05mmol) and *p*-trifluoromethylphenyl isocyanate (9 mg, 0.05mmol) following the procedure outlined in example 435. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.83 (s, 1H), 7.65 (d, J=8.2Hz, 2H), 7.53 (d, J=8.2Hz, 2H), 7.45 (d, J=6.9Hz, 1H), 7.39-7.32 (m, 5H), 7.20 (t, J=7.0Hz, 1H), 7.10-7.06 (m, 2H), 4.50 (m, 1H), 3.70-3.66 (m, 2H), 3.21 (br, 4H), 2.46 (s, 3H), 2.34-2.29 (m, 2H), 2.11-2.07 (m, 2H), 1.84-1.71 (m, 10H), 1.55 (d, J=7.5Hz, 2H). HRMS *m/z* $(M+H)^+$ calcd: 616.3263, obsd: 616.3258.

Example 440

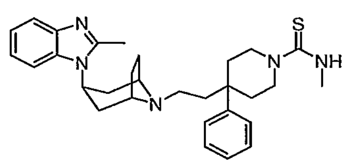
Preparation of N-isopropyl-4-{2-[3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo [3.2.1]oct-8-yl]ethyl}-4-phenylpiperidine-1-carbothioamide



N-Isopropyl-4-{2-[3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidine-1-carbothioamide (28 mg, quant.) was obtained as an oil from 2-methyl-1-{8-[2-(4-phenylpiperidin-4-yl)ethyl]-8-azabicyclo[3.2.1]-oct-3-yl}-1*H*-benzimidazole (22 mg, 0.05 mmol) and isopropyl isothiocyanate (5.5 mg, 0.05 mmol) following the procedure outlined in example 435. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.46 (d, J=7.1 Hz, 1 H), 7.37-7.32 (m, 5 H), 7.20-7.15 (m, 2 H), 7.11-7.05 (m, 2 H), 4.53-4.45 (m, 1 H), 4.00-3.97 (m, 2 H), 3.48-3.43 (m, 2 H), 3.20 (br, 2 H), 2.46 (s, 3 H), 2.36-2.28 (m, 2 H), 2.06-2.01 (m, 2 H), 1.82-1.70 (m, 10 H), 1.55 (d, J=7.5 Hz, 2 H). 1.09 (d, J=6.6 Hz, 6 H). HRMS *m/z* (M+H)$^+$ calcd: 530.3317, obsd: 530.3310.

Example 441

Preparation of N-methyl-4-{2-[3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo 3.2.1]oct-8-yl]ethyl}-4-phenylpiperidine-1-carbothioamide

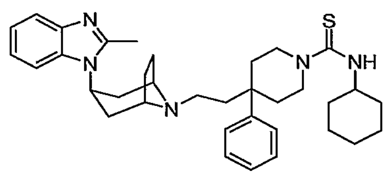


N-Methyl-4-{2-[3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenyl piperidine-1-carbothioamide (23 mg, 92%) was obtained as an oil from 2-methyl-1-{8-[2-(4-phenylpiperidin-4-yl)ethyl]-8-azabicyclo[3.2.1]-oct-3-yl}-1*H*-benzimidazole (22 mg, 0.05 mmol) and methyl isothiocyanate (4 mg, 0.055 mmol) following the procedure outlined in example 435. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.57 (d, J=4.1Hz,

1H), 7.46 (d, J=7.1Hz, 1H), 7.38-7.27 (m, 5H), 7.19 (t, J=6.8Hz, 1H), 7.11-7.05 (m, 2H), 4.54-4.44 (m, 1H), 4.02-3.97 (m, 2H), 3.46-3.41 (m, 2H), 3.20 (br, 2H), 2.86 (d, J=3.9Hz, 3H), 2.46 (s, 3H), 2.41-2.28 (m, 2H), 2.07-2.03 (m, 2H), 1.91-1.70 (m, 10H), 1.55 (d, J=7.5Hz, 2H). HRMS *m/z* $(M+H)^+$ calcd: 502.3004, obsd: 502.2994.

Example 442

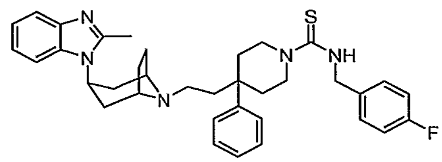
Preparation of N-cyclohexyl-4-{2-[3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo [3.2.1]oct-8-yl]ethyl}-4-phenylpiperidine-1-carbothioamide



N-Cyclohexyl-4-{2-[3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidine-1-carbothioamide (26.9mg, 94%) was obtained as an oil from 2-methyl-1-{8-[2-(4-phenylpiperidin-4-yl)ethyl]-8-azabicyclo[3.2.1]-oct-3-yl}-1*H*-benzimidazole (22mg, 0.05mmol) and cyclohexyl isothiocyanate (7.7mg, 0.05mmol) following the procedure outlined in example 435. ^1H NMR (400 MHz, DMSO-d_6) δ 7.46 (d, J=7.2 Hz, 1 H), 7.37-7.32 (m, 5 H), 7.20-7.17 (m, 1 H), 7.13-7.05 (m, 3 H), 4.51-4.47 (m, 1 H), 4.14 (br, 1 H), 4.00-3.97 (m, 2 H), 3.45 (t, J=9.7 Hz, 2 H), 3.20 (br, 2 H), 2.46 (s, 3 H), 2.36-2.28 (m, 2 H), 2.05-2.01 (m, 2 H), 1.82-1.67 (m, 15 H), 1.55 (d, J=7.8 Hz, 2 H). 1.23-1.15 (m, 4 H). HRMS *m/z* $(M+H)^+$ calcd: 570.3630, obsd: 570.3629.

Example 443

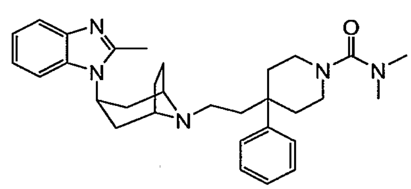
Preparation of N-(4-fluorobenzyl)-4-{2-[3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidine-1-carbothioamide



N-(4-Fluorobenzyl)-4-{2-[3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidine-1-carbothioamide (27.6mg, 93%) was obtained as an oil from 2-methyl-1-{8-[2-(4-phenylpiperidin-4-yl)ethyl]-8-azabicyclo[3.2.1]-oct-3-yl}-1*H*-benzimidazole (22mg, 0.05mmol) and 4-fluorobenzyl isothiocyanate (9.0mg, 0.054mmol) following the procedure outlined in example 435. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.13 (t, J=5.4 Hz, 1 H), 7.46 (d, J=7.5 Hz, 1 H), 7.39-7.30 (m, 5 H), 7.29-7.26 (m, 2 H), 7.20 (t, J=6.8 Hz, 1 H), 7.11-7.05 (m, 4 H), 4.73 (d, J=5.5 Hz, 2 H), 4.51-4.47 (m, 1 H), 4.07 (br, 2 H), 3.51 (t, J=9.9 Hz, 2 H), 3.21 (br, 2 H), 2.46 (s, 3 H), 2.41-2.29 (m, 2 H), 2.09-2.05 (m, 2 H), 1.83-1.71 (m, 10 H), 1.56 (d, J=7.7 Hz, 2 H). HRMS *m/z* $(M+H)^+$ calcd: 596.3223, obsd: 596.3232.

Example 444

Preparation of N,N-dimethyl-4-{2-[3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidine-1-carboxamide

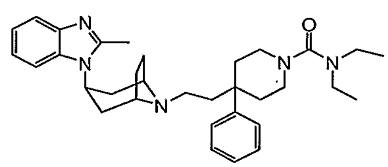


At 0 °C, to a stirred solution of phosgen (0.25 mL, 2.0 in toluene) was added a solution of 2-methyl-1-{8-[2-(4-phenylpiperidin-4-yl)ethyl]-8-azabicyclo[3.2.1]-oct-3-yl}-1*H*-benzimidazole (71 mg, 0.17mmol) in methylene chloride and triethylamine (excess). The mixture was stirred for 30 minutes at 0 °C and further one hour at room temperature. Nitrogene gas was then introduced to remove the excess phosgen. To this mixture was added

excess dimethylamine and the resulting mixture was stirred overnight at ambient temperature. After being diluted with methylene chloride, the organic phase was washed with brine, dried over anhydrous sodium sulfate and purified by flash chromatography. *N,N*-dimethyl-4-{2-[3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl] ethyl}-4-phenylpiperidine-1-carboxamid was obtained as foam (52 mg, 63%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (d, J=7.3 Hz, 1 H), 7.37-7.34 (m, 2 H), 7.31-7.29 (m, 3 H), 7.23-7.12 (m, 3 H), 4.61 (br, 1 H), 3.44-3.38 (m, 2 H), 3.25 (br, 2 H), 3.12-3.06 (m, 2 H), 2.80 (s, 6 H), 2.58 (s, 3 H), 2.38-2.36 (m, 2 H), 2.19-2.15 (m, 2 H), 1.93-1.81 (m, 10 H), 1.61 (d, J=7.3 Hz, 2 H). HRMS *m/z* $(M+H)^+$ calcd: 500.3389, obsd: 500.3386.

Example 445

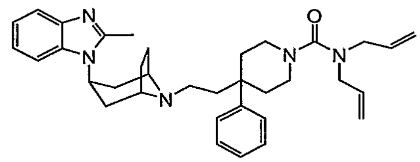
Preparation of N,N-diethyl-4-{2-[3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidine-1-carboxamide



N, N-Diethyl-4-{2-[3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidine-1-carboxamide (50 mg, 57%) was obtained as an oil from 2-methyl-1-{8-[2-(4-phenyl piperidin-4-yl)ethyl]-8-azabicyclo[3.2.1]-oct-3-yl}-1*H*-benzimidazole (71 mg, 0.17mmol), phosgen and diethylamine following the procedure outlined in example 444. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (d, J=7.3 Hz, 1 H), 7.37-7.29 (m, 5H), 7.23-7.12 (m, 3 H), 4.64-4.58 (m, 1 H), 3.41-3.35 (m, 2 H), 3.24-3.23 (m, 2 H), 3.17 (q, J=7.2 Hz, 4 H), 3.10-3.04 (m, 2 H), 2.57 (s, 3 H), 2.40-2.32 (m, 2 H), 2.19-2.15 (m, 2 H), 1.94-1.80 (m, 10 H), 1.60 (d, J=7.7 Hz, 2 H), 1.10 (t, J=7.0 Hz, 6 H). HRMS *m/z* $(M+H)^+$ calcd: 528.3702, obsd: 528.3712.

Example 446

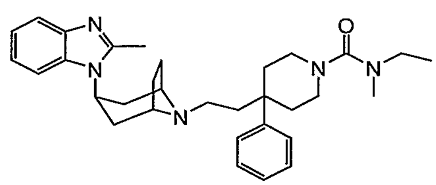
Preparation of N, N-diallyl-4-{2-[3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidine-1-carboxamide



N, N-Diallyl-4-{2-[3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidine-1-carboxamide (42 mg, 46%) was obtained as an oil from 2-methyl-1-{8-[2-(4-phenylpiperidin-4-yl)ethyl]-8-azabicyclo[3.2.1]-oct-3-yl}-1*H*-benzimidazole (71 mg, 0.17 mmol), phosgen and diallylamine following the procedure outlined in example 444. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (d, J=7.1 Hz, 1 H), 7.37-7.33 (m, 2 H), 7.30-7.29 (m, 3 H), 7.23-7.12 (m, 3 H), 5.86-5.76 (m, 2 H), 5.18-5.13 (m, 4 H), 4.61 (br, 1 H), 3.72 (d, J=5.5Hz, 4 H), 3.47-3.41 (m, 2 H), 3.24 (br, 2 H), 3.12-3.06 (m, 2 H), 2.57 (s, 3 H), 2.40-2.32 (m, 2 H), 2.20-2.15 (m, 2 H), 1.99-1.80 (m, 10 H), 1.60 (d, J=7.7 Hz, 2 H). HRMS *m/z* $(M+H)^+$ calcd: 552.3702, obsd: 552.3701.

Example 447

Preparation of N-ethyl-N-methyl-4-{2-[3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidine-1-carboxamide

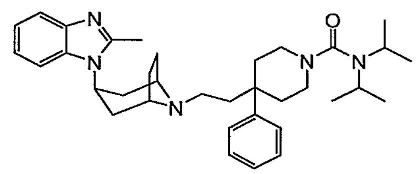


N-Ethyl-*N*-methyl-4-{2-[3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidine-1-carboxamide (53 mg, 62%) was obtained as an oil from 2-methyl-1-{8-[2-(4-phenylpiperidin-4-yl)ethyl]-8-azabicyclo[3.2.1]-oct-3-yl}-1*H*-benzimidazole (71 mg, 0.17mmol), phosgen and *N*-ethyl-*N*-methylamine following the procedure outlined in example 444. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (d, J=7.1 Hz, 1 H), 7.37-7.33

(m, 2 H), 7.31-7.29 (m, 3 H), 7.23-7.12 (m, 3 H), 4.63-4.59 (m, 1 H), 3.41-3.36 (m, 2 H), 3.24 (br, 2 H), 3.18 (q, J=7.1 Hz, 2 H), 3.11-3.04 (m, 2 H), 2,77 (s, 3 H), 2.57 (s, 3 H), 2.40-2.32 (m, 2 H), 2.19-2.15 (m, 2 H), 1.99-1.80 (m, 10 H), 1.60 (d, J=7.9 Hz, 2 H), 1.12 (t, J=7.1 Hz, 3 H). HRMS *m/z* $(M+H)^+$ calcd: 514.3546, obsd: 514.3526.

Example 448

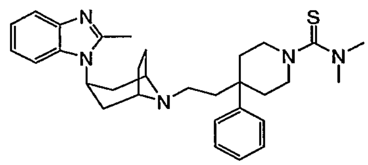
Prearation of N,N-diisopropyl-4-{2-[3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidine-1-carboxamide



To a flask containing phosgen (2 mL, 2 M in toluene) in methylene chloride (10 mL) was added triethylamine (75 μL, 0.5 mmol) and diisopropylamine (76 μL, 0.5 mmol). The mixture was stirred at room temperature for 4 hours before nitrogen gas was introduced to remove excess phosgen. To this freshly prepared chlorodiisopropyl carbamate was added 2-methyl-1-{8-[2-(4-phenylpiperidin-4-yl)ethyl]-8-azabicyclo[3.2.1]-oct-3-yl}-1*H*-benzimidazole (85 mg, 0.2 mmol) and triethylamin (60 μL, 0.4 mmol). The resulting mixture was stirred overnight at ambient temperature. The excess chlorocarbamate was quenched with 1 mL of methanol. After evaporation of solvent, the residue was directly purified by flash chromatography, eluting with a gradient of 0-5% methanol in ethyl acetate, to afford an oil (81 mg, 73%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (d, J=7.4 Hz, 1 H), 7.37-7.33 (m, 2 H), 7.31-7.30 (m, 3 H), 7.22-7.12 (m, 3 H), 4.63-4.59 (m, 1 H), 3.62-3.55 (m, 2 H), 3.29-3.23 (m, 4 H), 3.03-2.97 (m, 2 H), 2.57 (s, 3 H), 2.40-2.32 (m, 2 H), 2.18-2.14 (m, 2 H), 1.95-1.80 (m, 10 H), 1.60 (d, J=7.9 Hz, 2 H), 1.26 (d, J=6.6 Hz, 6 H). HRMS *m/z* $(M+H)^+$ calcd: 556.4015, obsd: 556.4008.

Example 449

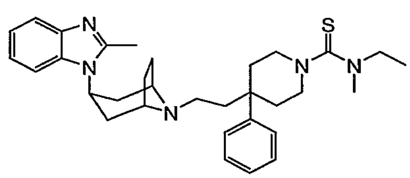
Preparation of N, N-dimethyl-4-{2-[3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidine-1-carbothioamide



N, N-Dimethyl-4-{2-[3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidine-1-carbothioamide (58 mg, 75%) was obtained as a foam from 2-methyl-1-{8-[2-(4-phenylpiperidin-4-yl)ethyl]-8-azabicyclo[3.2.1]-oct-3-yl}-1*H*-benzimidazole dihydrochloride (75 mg, 0.15mmol), thiophosgen and dimethylamine following the procedure outlined in example 444. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (d, J=7.1 Hz, 1 H), 7.45-7.35 (m, 2 H), 7.32-7.29 (m, 3 H), 7.25-7.19 (m, 1 H), 7.17-7.12 (m, 2 H), 4.63-4.58 (m, 1 H), 3.75-3.70 (m, 2 H), 3.32-3.24 (m, 4 H), 3.10 (s, 6 H), 2.58 (s, 3 H), 2.40-2.33 (m, 2 H), 2.26-2.22 (m, 2 H), 1.97-1.82 (m, 10 H), 1.61 (d, J=7.9 Hz, 2 H). HRMS *m/z* $(M+H)^+$ calcd: 516.3161, obsd: 516.3158.

Example 450

Prearation of N-ethyl-N-methyl-4-{2-[3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidine-1-carbothioamide

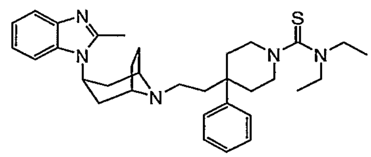


N-Ethyl-*N*-methyl-4-{2-[3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidine-1-carbothioamide (62 mg, 78%) was obtained as a foam from 2-methyl-1-{8-[2-(4-phenyl piperidin-4-yl)ethyl]-8-azabicyclo[3.2.1]-oct-3-yl}-1*H*-benzimidazole dihydrochloride (75 mg, 0.15mmol), thiophosgen and *N*-ethyl-*N*-methylamine following the procedure outlined in example 444. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (d, J=7.2 Hz, 1 H), 7.38-7.34 (m, 2 H), 7.31-7.29 (m, 3 H), 7.24-7.21 (m, 1 H),

7.18-7.12 (m, 2 H), 4.63-4.58 (m, 1 H), 3.72-3.66 (m, 2 H), 3.61 (q, J=7.0 Hz, 2 H), 3.31-3.24 (m, 4 H), 3.03 (s, 3 H), 2.57 (s, 3 H), 2.40-2.32 (m, 2 H), 2.26-2.21 (m, 2 H), 1.97-1.82 (m, 10 H), 1.60 (d, J=7.8 Hz, 2 H), 1.21 (t, J=7.1 Hz, 3 H). HRMS *m/z* $(M+H)^+$ calcd: 530.3317, obsd: 530.3301.

Example 451

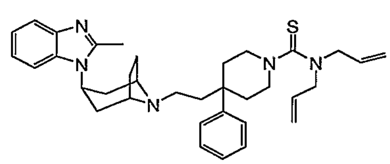
Preparation of N, N-diethyl-4-{2-[3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidine-1-carbothioamide



N,N-Diethyl-4-{2-[3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidine-1-carbothioamide (51 mg, 62%) was obtained as a foam from 2-methyl-1-{8-[2-(4-phenylpiperidin-4-yl)ethyl]-8-azabicyclo[3.2.1]-oct-3-yl}-1*H*-benzimidazole dihydrochloride (75 mg, 0.15mmol), thiophosgen and diethylamine following the procedure outlined in example 444. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (d, J=7.4 Hz, 1 H), 7.38-7.34 (m, 2 H), 7.32-7.29 (m, 3 H), 7.25-7.21 (m, 1 H), 7.19-7.12 (m, 2 H), 4.63-4.59 (m, 1 H), 3.72-3.68 (m, 2 H), 3.57 (q, J=7.1 Hz, 4 H), 3.30-3.25 (m, 4 H), 2.58 (s, 3 H), 2.40-2.33 (m, 2 H), 2.25-2.21 (m, 2 H), 1.97-1.82 (m, 10 H), 1.61 (d, J=7.7 Hz, 2 H), 1.18 (t, J=7.1 Hz, 6 H). HRMS *m/z* $(M+H)^+$ calcd: 544.3474, obsd: 544.3482.

Example 452

Preparation of N, N-diallyl-4-{2-[3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidine-1-carbothioamide

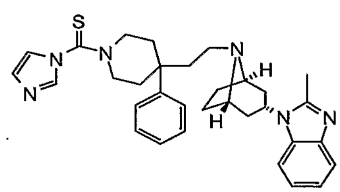


N, N-Diallyl-4-{2-[3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidine-1-carbothioamide (55 mg,

65%) was obtained as a foam from 2-methyl-1-{8-[2-(4-phenylpiperidin-4-yl)ethyl]-8-azabicyclo[3.2.1]-oct-3-yl}-1H-benzimidazole dihydrochloride (75 mg, 0.15 mmol), thiophosgen and diallylamine following the procedure outlined in example 444. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (d, J=7.1 Hz, 1 H), 7.38-7.35 (m, 2 H), 7.31-7.29 (m, 3 H), 7.25-7.21 (m, 1 H), 7.19-7.12 (m, 2 H), 5.91-5.81 (m, 2 H), 5.23-5.17 (m, 4 H), 4.63-4.58 (m, 1 H), 4.10 (d, J=5.6 Hz, 4 H), 3.82-3.79 (m, 2 H), 3.35-3.25 (m, 4 H), 2.59 (s, 3 H), 2.40-2.32 (m, 2 H), 2.27-2.23 (m, 2 H), 1.97-1.80 (m, 10 H), 1.61 (d, J=7.9 Hz, 2 H). HRMS *m/z* $(M+H)^+$ calcd: 568.3474, obsd: 568.3470.

Example 453

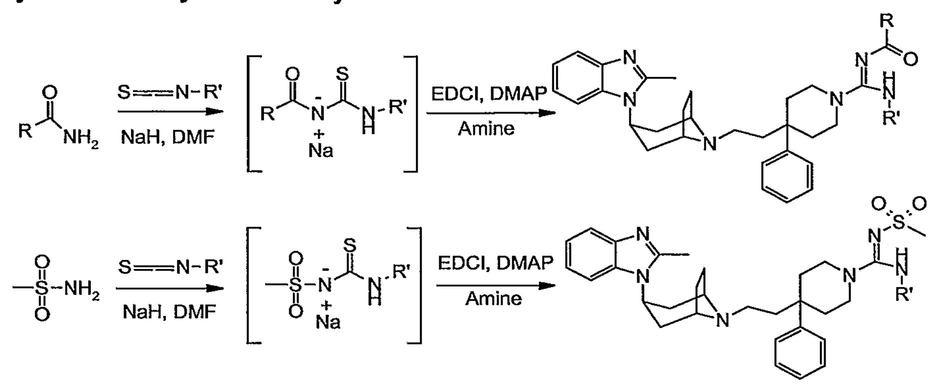
Preparation of 1-((1R,5S)-8-{2-[1-(1H-imidazol-1-ylcarbonothioyl)-4-phenylpiperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1H-benzimidazole



To a stirred solution of 2-methyl-1-{8-[2-(4-phenylpiperidin-4-yl)ethyl]-8-azabicyclo[3.2.1]-oct-3-yl}-1*H*-benzimidazole (214 mg, 0.5 mmol) in methylene chloride was added 1-(1*H*-imidazol-1-ylcarbonothioyl)-1*H*-imidazole (89 mg, 0.5 mmol). The resulting mixture was stirred overnight. After evaporation of the solvents, the crude product was purified by flash chromatography, eluting with a gradient of 0-5% methanol in ethyl acetate, to afford 1-((1*R*, 5*S*)-8-{2-[1-(1*H*-imidazol-1-ylcarbonothioyl)-4-phenylpiperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1*H*-benzimidazole as a foam (200 mg, 74%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (s, 1 H), 7.65 (d, J=7.1 Hz, 1 H), 7.42-7.39 (m, 2 H), 7.31-7.28 (m, 4 H), 7.19-7.10 (m, 3 H), 7.07 (s, 1 H), 4.62-4.56 (m, 1 H), 3.53 (br, 1 H), 3.24-3.22 (m, 2 H), 2.56 (s, 3 H), 2.40-2.32 (m, 4 H), 1.99-1.81 (m, 10, H), 1.62 (d, J=7.9 Hz, 2 H). HRMS *m/z* $(M+H)^+$ calcd: 539.2957, obsd: 539.2958.

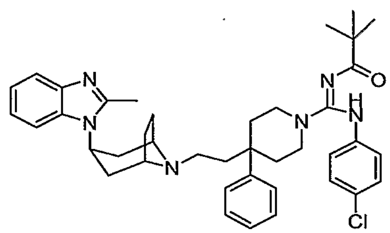
Preparation of N-acyl and N-sulfonyl guanidine Derivatives of 2-Methyl-1-{8-[2-(4-Phenylpiperidin-4-yl)ethyl]-8-Azabicyclo[3.2.1]-oct-3-yl}-1H-benzimidazole

Synthesis of Acyl and Sulfonyl Derivatives



Example 454

Preparation of N-[(1E)-[(4-chlorophenyl)amino](4-{2-[3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)methylidene]-2,2-dimethylpropanamide

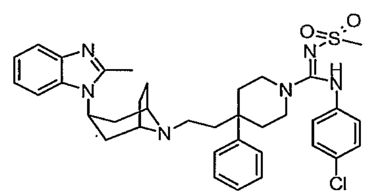


To a solution of trimethylacetamide (10 mg, 0.1 mmol) in DMF (0.5 mL) was added sodium hydride (60%, 5.2 mg, 0.13 mmol). After stirring for 5 minutes, 4-chlorophenylisothiocyanate (17 mg, 0.1 mmol) was added. The reaction mixture was stirred at 60 °C for one hour before being cooled down to room temperature. To this reaction mixture was then added 2-methyl-1-{8-[2-(4-phenylpiperidin-4-yl)ethyl]-8-azabicyclo[3.2.1]-oct-3-yl}-1*H*-benzimidazole (35 mg, 0.08mmol), EDCI (19 mg, 0.1 mmol) and a catalytic amount of DMAP. After stirring at ambient temperature overnight, the reaction was quenched with water and extracted with dichloromethane (4x10 mL). The organic phase was washed with brine and dried over sodium sulfate. The solvent was removed and the residue was purified by flash chromatography on silical gel,

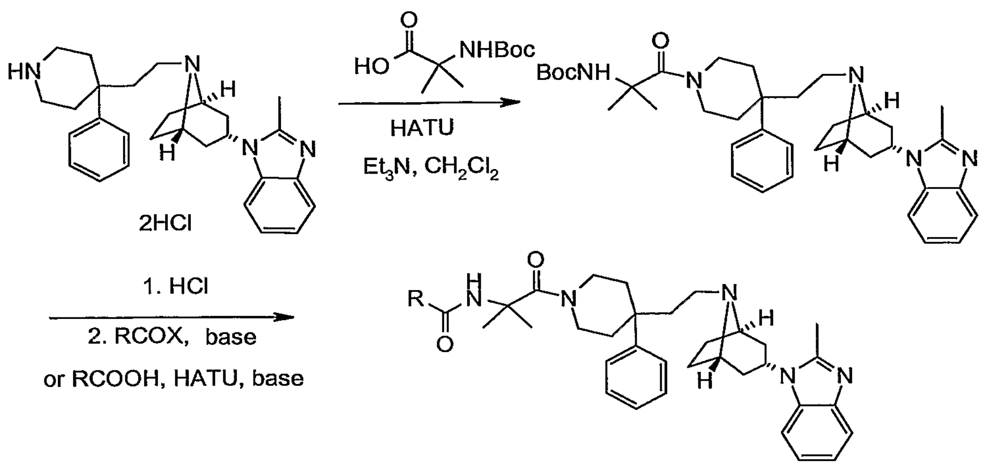
eluting with a gradient of 0-15% methanol in ethyl acetate to afford *N*-[(1*E*)-[(4-chlorophenyl)amino](4-{2-[3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo [3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl) methylidene]-2,2-dimethylpropanamide as amorphous solid (20 mg, 38%). ^{1}H NMR (400 MHz, DMSO-d$_6$) δ 8.9 (s, 1 H), 7.46 (d, J=8.8 Hz, 1 H), 7.39-7.33 (m, 6 H), 7.22-7.19 (m, 1 H), 7.13-7.05 (m, 3 H), 6.61 (d, J=8.6 Hz, 2 H), 4.51-4.47 (m, 1 H), 3.80-3.40 (m, 2 H), 3.26-3.13 (m, 4 H), 2.46 (s, 3 H), 2.37-2.30 (m, 2 H), 2.14 (br, 2 H), 1.85-1.71 (m, 10 H), 1.56 (d, J=7.4 Hz, 2 H), 0.88 (s, 9 H). HRMS *m/z* (M+H)$^+$ calcd: 665.3735, obsd: 665.3741.

Example 455

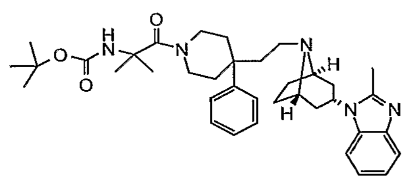
Preparation of N-[(1E)-[(4-chlorophenyl)amino](4-{2-[3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)methylidene]methane-sulfonamide



N-[(1*E*)-[(4-Chlorophenyl)amino](4-{2-[3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)methylidene] methanesulfonamide (38 mg, 73%) was obtained as amorphous solid from methanesulfonamide (9.5 mg, 0.1 mmol), 4-chloropheyl isothiocyanate (17 mg, 0.1 mmol) and 2-methyl-1-{8-[2-(4-phenylpiperidin-4-yl)ethyl]-8-azabicyclo[3.2.1]-oct-3-yl}-1*H*-benzimidazole (35 mg, 0.08mmol) following the procedure outlined in example 454. ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.39 (s, 1H), 7.64 (d, J=7.1 Hz, 1H), 7.37-7.33 (m, 2H), 7.30-7.21 (m, 6H), 7.19-7.10 (m, 2H), 6.89 (d, J=8.6 Hz, 2H), 4.59-4.53 (m, 1H), 3.61 (d, J=13.5 Hz, 2H), 3.19 (br, 2H), 3.04 (t, J=11 Hz, 2H), 2.96 (s, 3H), 2.53 (s, 3H), 2.37-2.29 (m, 2 H), 2.20-2.16 (m, 2 H), 1.90-1.84 (m, 6H), 1.82-1.71 (m, 4H), 1.58 (d, J=7.4 Hz, 2H). HRMS *m/z* (M+H)$^+$ calcd: 659.2935, obsd: 659.2935.



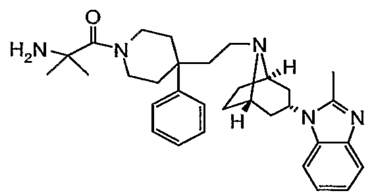
Example 456



To a stirred solution of 2-methyl-1-{8-[2-(4-phenylpiperidin-4-yl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1*H*-benzimidazole dihydrochloride (505 mg, 1.0 mmol) in dichoromethane (20 mL) was added Boc-α-methyl alanine (203 mg, 1.0 mmol), triethylamine (470 μL, 3.0 mmol) and HATU (380 mg, 1.0 mmol). The resulting mixture was stirred at ambient temperature overnight before being quenched with saturated sodium bicarbonate. The layers were separated and the aqueous was extracted with dichloromethane. The combined organic phase was dried over anhydrous sodium sulfate. After evaporation of the solvent, the crude product was purified by flash chromatography on silical gel, eluting with a gradient of 0-8% methanol in ethyl acetate to afford compound 456 as amorphous solid (579 mg, 94%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (d, J=7.1 Hz, 1 H), 7.38-7.34 (m, 1 H), 7.30-7.20 (m, 3 H), 7.19-7.13 (m, 3 H), 5.04 (s, 1 H), 4.65-4.61 (m, 1 H), 4.09-4.02 (m, 2H), 3.29-3.20 (m, 5 H), 2.58 (s, 3 H), 2.44-2.36 (m, 2 H), 2.22-2.20 (m, 2 H), 1.95-1.89 (m, 5 H), 1.84-1.78 (m, 4 H), 1.64 (d, J=7.8 Hz, 2 H), 1.49 (s, 5 H), 1.39-1.35 (m, 10 H). HRMS *m/z* $(M+H)^+$ calcd: 614.4070, obsd: 614.4086.

Example 457

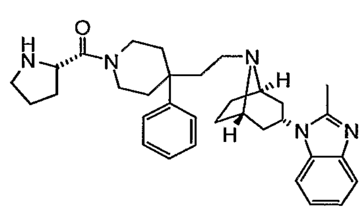
Preparation of 2-methyl-1-(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)-1-oxopropan-2-amine



To a stirred solution of the product from example 456 (307 mg, 0.50 mmol) in methylene chloride was added HCl (2 mL, 4 M in dioxane). The reaction mixture was stirred for one hour at ambient temperature. Evaporation of solvents directly afforded 240 mg (99%) of white solid, which was then partitioned between ethyl acetate and saturated sodium bicarbonate solution. The organic phase was dried over anhydrous sodium sulfate. After removal of the solvent, the desired product was obtained as foam. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (d, J=7.1 Hz, 1 H), 7.39-7.35 (m, 2 H), 7.31-7.22 (m, 4 H), 7.19-7.12 (m, 2 H), 4.64 (m, 1 H), 4.13-4.11 (m, 2 H), 3.40 (br, 2 H), 3.27 (br, 2 H), 2.57 (s, 3 H), 2.52-2.24 (m, 4 H), 1.94-1.91 (m, 4 H), 1.88-1.68 (m, 8 H), 1.63 (d, J=7.9 Hz, 2 H), 1.41 (s, 6 H). HRMS *m/z* $(M+H)^+$ calcd: 514.3546, obsd: 514.3561.

Example 458

Preparation of (2S)-N,N-bis(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenyl-1-D-prolylpiperidin-2-yl)-D-prolinamide

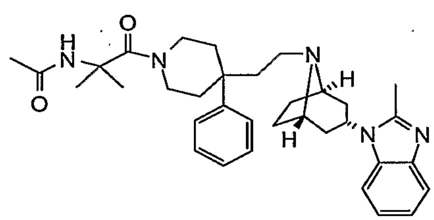


The Boc protected precursor was prepared from *L*-Boc–proline (47 mg, 0.15 mmol), 2-methyl-1-{8-[2-(4-phenylpiperidin-4-yl)ethyl]-8-

azabicyclo[3.2.1]oct-3-yl}-1*H*-benzimidazole (64 mg, 0.15 mmol) and HATU (57 mg, 0.15 mmol), following the procedure outlined in example 456. After removal of Boc protecting group with a solution of 4N HCl in dioxane, (2*S*)-*N*, *N*- bis(4-{2-[(1*R*, 5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenyl-1-*D*-prolyl-piperidin-2-yl)-*D*-prolinamide was obtained as an oil (80 mg, quant.). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (d, J=7.4 Hz, 1 H), 7.40-7.36 (m, 2 H), 7.30-7.28 (m, 3 H), 7.25-7.23 (m, 1 H), 7.21-7.12 (m, 2 H), 4.65-4.55 (m, 1 H), 4.11-4.02 (m, 1 H), 3.93-3.84 (m, 1 H), 3.68-3.63 (m, 1 H), 3.32-3.14 (m, 5 H), 2.85-2.73 (m, 1 H), 2.57 (s, 3 H), 2.40-2.24 (m, 6 H), 2.15-1.50 (m, 5 H). HRMS *m/z* $(M+H)^+$ calcd: 526.3546, obsd: 526.3565.

Example 459

Preparation of N^2-acetyl-N^1, N^1-bis(1-(N-acetyl-2-methylalanyl)-4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-2-yl)-2-methylalaninamide

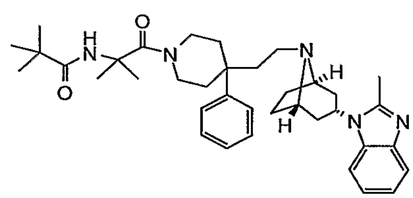


At 0 °C, to a stirred solution of 2-methyl-1-(4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)-1-oxopropan-2-amine dihydrochloride (40 mg, 0.068mmol, obtained from compound 456 by removal of Boc protecting group with 4 M HCl in ether) in dichoromethane was added acetyl bromide (8.6 mg, 0.068 mmol), *N,N*-diethyl-isopropylamine (42 μL, 0.24 mmol) and DMAP (1 mg). The resulting mixture was stirred for 3 hours before being quenched with saturated sodium bicarbonate. The layers were separated and the aqueous layer was extracted with dichloromethane. The combined organic phase was dried over anhydrous sodium sulfate. After evaporation of the solvent, the crude product was purified by flash chromatography on silical gel, eluting with a

gradient of 0-10% methanol in ethyl acetate to afford *N*^{2}-acetyl-*N*^{1}, *N*^{1}-bis(1-(*N*-acetyl-2-methylalanyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-2-yl)-2-methylalaninamide as amorphous solid (34 mg, 90%). ^{1}H NMR (400 MHz, $CDCl_3$), δ 7.67 (d, J=6.5 Hz, 1 H), 7.40-7.37 (m, 2 H), 7.30-7.26 (m, 3 H), 7.24-7.13 (m, 3 H), 7.07 (s, 1 H), 4.03-4.00 (m, 1 H), 3.67-3.61 (m, 2 H), 3.34 (t, J=7.8 Hz, 1 H), 3.08 (q, J=7.3 Hz, 1 H), 2.79-2.61 (m, 4 H), 2.43-2.08 (m, 6 H), 2.06-1.92 (m, 4 H), 1.85-1.80 (m, 2 H), 1:58 (s, 3 H), 1.54 (s, 3 H), 1.52-1.51 (m, 4 H), 1.43 (d, J=6.6 Hz, 4H). HRMS *m/z* $(M+H)^+$ calcd: 556.3651, obsd: 556.3647.

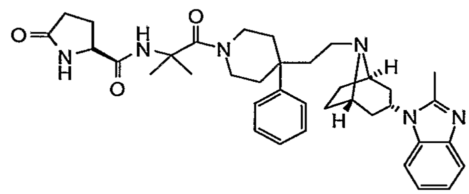
Example 460

Preparation of N^2-(2,2-dimethylpropanoyl)-N^1,N^1-bis(1-[N-(2,2-dimethylpropanoyl)-2-methylalanyl]-4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-2-yl)-2-methylalaninamide



N^2-(2,2-dimethylpropanoyl)-*N*^{1},*N*^{1}-bis(1-[*N*-(2,2-dimethylpropanoyl)-2-methylalanyl]-4-{2-[(1*R*, 5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1] oct-8-yl]ethyl}-4-phenylpiperidin-2-yl)-2-methyl alaninamide (17 mg, 42%) was obtained as an oil from 2-methyl-1-(4-{2-[(*1R,5S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenyl piperidin-1-yl)-1-oxopropan-2-amine dihydrochloride (40 mg, 0.068 mmol) and pivaloyl chloride (8.4 μL, 0.068 mmol) following the procedure outlined in the example 459. ^{1}H NMR (400 MHz, $CDCl_3$), δ 7.66 (d, J=7.1 Hz, 1 H), 7.40-7.36 (m, 2 H), 7.30-7.23 (m, 4 H), 7.19-7.12 (m, 2 H), 4.61 (br, 1 H), 3.99 (br, 2 H), 3.32-3.26 (m, 4 H), 2.57 (s, 3 H), 2.41-2.23 (m, 4 H), 1.93-1.76 (m, 9 H), 1.65 (s, 6 H), 1.63-1.61 (m, 2 H), 1.19 (s, 9 H). HRMS *m/z* $(M+H)^+$ calcd: 598.4121, obsd: 598.4116.

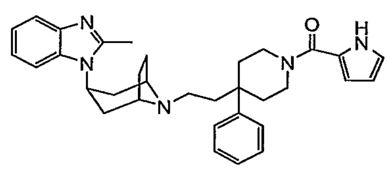
Example 461



The product in example 461 (9 mg, 29 %) was obtained from 2-methyl-1-(4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)-1-oxopropan-2-amine dihydrochloride (26 mg, 0.05mmol), 5-oxo-*D*-proline (6.5 mg, 0.05mmol) and HATU (19 mg, 0.05mmol) following the procedure outlined in example 5. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79(s, 1 H), 7.65 (d, J=7.2 Hz, 1 H), 7.40-7.36 (m, 2 H), 7.30-7.23 (m, 4 H), 7.19-7.12 (m, 2 H), 6.72 (s, 1 H), 4.63-4.58 (m, 1 H), 4.14-4.09 (m, 1 H), 3.97 (br, 2 H), 3.31-3.25 (m, 4 H), 2.57 (s, 3 H), 2.54-2.10 (m, 9 H), 1.93-1.75 (m, 10 H), 1.67-1.60 (m, 8 H). HRMS *m/z* $(M+H)^+$ calcd: 625.3866, obsd: 625.3863.

Example 462

Preparation of 2-Methyl-1-(8-{2-[4-phenyl-1-(1H-pyrrol-2-ylcarbonyl)piperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-1H-benzimidazole

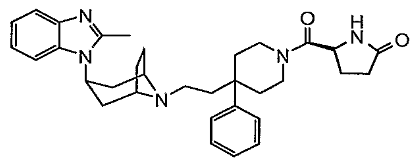


2-Methyl-1-(8-{2-[4-phenyl-1-(1*H*-pyrrol-2-ylcarbonyl)piperidin-4-yl]ethyl}-8-azabicyclo[3.2.1] oct-3-yl)-1*H*-benzimidazole (58.5 mg, 75%) was obtained as a white solid from 2-methyl-1-{8-[2-(4-phenyl piperidin-4-yl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1*H*-benzimidazole (64 mg, 0.15 mmol), 1*H*-pyrrole-2-carboxylic acid (16.6 mg, 0.15 mmol) and HATU (57 mg, 0.15 mmol), following the procedure outlined in example 5. ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.5 (br, 1 H), 7.68 (s, 1 H), 7.53-7.46 (m, 2 H), 7.41-7.32 (m, 5 H), 7.22-7.18 (m, 1 H), 7.13-7.04 (m, 3 H), 4.53-4.47 (m, 1 H), 4.11 (br, 1 H),

3.85 (br, 1 H), 3.27-3.09 (m, 4 H), 2.46 (s, 3 H), 2.39-2.29 (m, 2 H), 2.0 (br, 2 H), 1.97-1.70 (m, 10 H), 1.57-1.55 (m, 2 H). HRMS *m/z* $(M+H)^+$ calcd: 522.3233, obsd: 522.3226.

Example 463

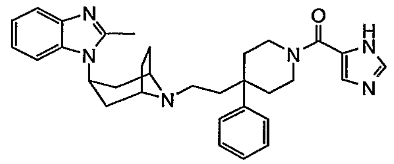
Preparation of (5R)-5-[(4-{2-[3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]pyrrolidin-2-one



(5*R*)-5-[(4-{2-[3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenyl piperidin-1-yl)carbonyl]pyrrolidin-2-one (59 mg, 85%) was obtained as white solid from 2-methyl-1-{8-[2-(4-phenylpiperidin-4-yl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1*H*-benzimidazole (64 mg, 0.15 mmol), 5-oxo-*D*-proline (19 mg, 0.15 mmol) and HATU (57 mg, 0.15 mmol), following the procedure outlined in example 5. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (d, J=8.8 Hz, 1 H), 7.40-7.36 (m, 2 H), 7.30-7.23 (m, 4 H), 7.18-7.11 (m, 2 H), 6.20 (s, ½ H), 6.09 (s, ½ H), 4.62-4.56 (m, 1 H), 4.50-4.42 (m, 1 H), 4.07-4.02 (m, 1 H), 3.58-3.55 (m, 1 H), 3.25-3.16 (m, 4 H), 2.56 (s, 3 H), 2.46-2.14 (m, 47 H), 2.03-1.73 (m, 11 H), 1.63-1.58 (m, 2 H). HRMS *m/z* $(M+H)^+$ calcd: 540.3339, obsd: 540.3361.

Example 464

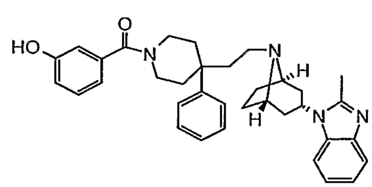
Preparation of 1-(8-{2-[1-(1H-imidazol-5-ylcarbonyl)-4-phenylpiperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1H-benzimidazole



1-(8-{2-[1-(1*H*-Imidazol-5-ylcarbonyl)-4-phenylpiperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1*H*-benzimidazole (18 mg, 23 %) was obtained from 2-methyl-1-{8-[2-(4-phenylpiperidin-4-yl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1*H*-benzimidazole (64 mg, 0.15 mmol), 1H-imidazole-5-carboxylic acid (17 mg, 0.15 mmol) and HATU (57 mg, 0.15 mmol), following the procedure outlined in example 5. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.68 (s, 1 H), 7.66 (d, J=8.6 Hz, 1 H), 7.41-7.23 (m, 6 H), 7.19-7.12 (m, 2 H), 6.90 (s, 1 H), 6.51 (s, 1 H), 6.24 (s, 1 H), 4.64-4.58 (m, 1 H), 4.20-4.14 (m, 2 H), 3.48 (br, 1 H), 3.25 (br, 2 H), 2.56 (s, 3 H), 2.41-2.28 (m, 4 H), 2.01-1.81 (m, 10 H), 1.64-1.58 (m, 2 H). HRMS *m/z* $(M+H)^+$ calcd: 523.3185, obsd: 523.3204.

Example 465

Preparation of 3-[(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]phenol

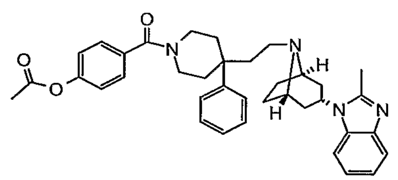


3-[(4-{2-[(1*R*, 5*S*)-3-(2-Methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]phenol (70 mg, 84 %) was obtained from 2-methyl-1-{8-[2-(4-phenylpiperidin-4-yl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1*H*-benzimidazole (64 mg, 0.15 mmol), 3-hydroxybenzoic acid (21 mg, 0.15 mmol) and HATU (57 mg, 0.15 mmol), following the procedure outlined in example 5. ^{1}H NMR (400 MHz, $CDCl_3$) δ

7.66 (d, J=6.9 Hz, 1 H), 7.39-7.35 (m, 2 H), 7.31-7.24 (m, 4 H), 7.21-7.13 (m, 3 H), 6.94 (s, 1 H), 6.88-6.85 (m, 1 H), 6.81 (d, J=7.5 Hz, 1 H), 4.64-4.55 (m, 1 H), 4.13 (br, 1 H), 3.59-3.56 (m, 1 H), 3.40-3.37 (m, 1 H), 3.27-3.24 (m, 3 H), 2.49 (s, 3 H), 2.44-2.34 (m, 2 H), 2.26 (br, 1 H), 2.18-2.15 (m, 1 H), 1.99-1.79 (m, 10 H), 1.63-1.61 (m, 2 H). HRMS *m/z* $(M+H)^+$ calcd: 549.3230, obsd: 549.3240.

Example 466

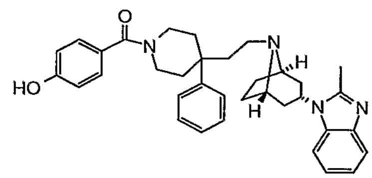
Preparation of 4-[(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]phenyl acetate



4-[(4-{2-[(1*R*, 5*S*)-3-(2-Methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]phenyl acetate (68 mg, 77 %) was obtained as a foam from 2-methyl-1-{8-[2-(4-phenylpiperidin-4-yl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1*H*-benzimidazole (64 mg, 0.15 mmol), 4-(acetyloxy) benzoic acid (27 mg, 0.15 mmol) and HATU (57 mg, 0.15 mmol), following the procedure outlined in example 5. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (d, J=8.4 Hz, 1 H), 7.41-7.33 (m, 4 H), 7.30-7.22 (m, 4 H), 7.21-7.08 (m, 4 H), 4.64-4.54 (m, 1 H), 4.10 (br, 1 H), 3.58 (br, 1 H), 3.36-3.24 (m, 4 H), 2.54 (s, 3 H), 2.39-2.34 (m, 3 H), 2.30 (s, 3 H), 2.14 (br, 21 H), 1.98-1.82 (m, 10 H), 1.60 (d, J=7.8 Hz, 2 H). HRMS *m/z* $(M+H)^+$ calcd: 591.3335, obsd: 591.3348.

Example 467

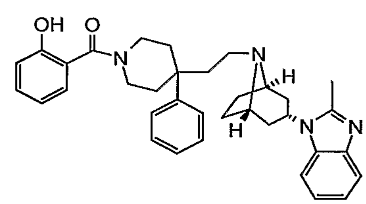
Preparation of 4-[(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]phenol



4-[(4-{2-[(1*R*, 5*S*)-3-(2-Methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]phenol (27 mg, 33%) was obtained as a foam from 2-methyl-1-{8-[2-(4-phenylpiperidin-4-yl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1*H*-benzimidazole (64 mg, 0.15 mmol), 4-hydroxylbenzoic acid (21 mg, 0.15 mmol) and HATU (57 mg, 0.15 mmol), following the procedure outlined in example 5. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67-7.64 (m, 1 H), 7.39-7.23 (m, 8 H), 7.23-7.13 (m, 2 H), 6.84 (d, J=8.4 Hz, 2 H), 4.67-4.54 (m, 1 H), 4.13 (br, 1 H), 3.71 (br, 1 H), 3.40-3.26 (m, 4 H), 2.51 (s, 3 H), 2.40-2.11 (m, 4 H), 1.95-1.82 (m, 10 H), 1.62 (d, J=8.0 Hz, 2 H). HRMS *m/z* $(M+H)^+$ calcd: 549.3230, obsd: 548.3233.

Example 468

Preparation of 2-[(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]phenol

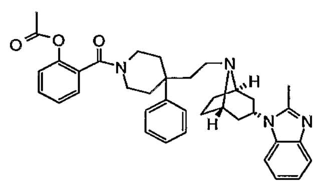


2-[(4-{2-[(1*R*, 5*S*)-3-(2-Methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]phenol (70 mg, 85%) was obtained as a syrupy from 2-methyl-1-{8-[2-(4-phenylpiperidin-4-yl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1*H*-benzimidazole (64 mg, 0.15 mmol), 2-hydroxylbenzoic acid (21 mg, 0.15 mmol) and HATU (57 mg, 0.15 mmol), following the procedure outlined in example 5. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.81 (s, 1 H), 7.65 (d, J=7.8 Hz, 1 H), 7.42-7.31 (m, 2 H), 7.30-7.11 (m, 8 H),

7.00 (d, J=8.1 Hz, 1 H), 6.83 (t, J=7.4 Hz, 1 H), 4.67-4.53 (m, 1 H), 4.07-4.02 (m, 4 H), 3.40 (t, J=10.7 Hz, 1 H), 3.25 (br, 2 H), 2.55 (s, 3 H), 2.42-2.29 (m, 4 H), 1.94-1.80 (m, 10 H), 1.63-1.58 (m, 2 H). HRMS *m/z* $(M+H)^+$ calcd: 549.3230, obsd: 548.3223.

Example 469

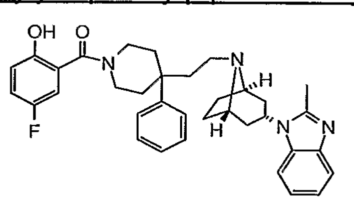
Preparation of 2-[(4-{2-[(1R, 5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]phenyl acetate



2-[(4-{2-[(1*R*, 5*S*)-3-(2-Methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]phenyl acetate (60 mg, 68%) was obtained as syrup from 2-methyl-1-{8-[2-(4-phenylpiperidin-4-yl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1*H*-benzimidazole (64 mg, 0.15 mmol), 2-(acetyloxy)benzoic acid (27 mg, 0.15 mmol) and HATU (57 mg, 0.15 mmol), following the procedure outlined in example 5. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (d, J=8.4 Hz, 1 H), 7.43-7.32 (m, 3 H), 7.30-7.23 (m, 6 H), 7.21-7.12 (m, 3 H), 4.62-4.56 (m, 1 H), 4.16-4.11 (m, 1 H), 3.46-3.34 (m, 2 H), 3.23-3.20 (m, 3 H), 2.53 (s, 3 H), 2.41-2.27 (m, 4 H), 2.16-2.13 (m, 2 H), 1.92-1.79 (m, 11 H), 1.62-1.57 (m, 2 H). HRMS *m/z* $(M+H)^+$ calcd: 591.3335, obsd: 591.3341.

Example 470

Preparation of 4-fluoro-2-[(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]phenol

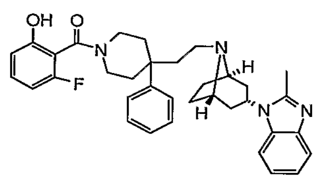


4-Fluoro-2-[(4-{2-[(1*R*, 5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]phenol (58 mg,

85%) was obtained as a foam from 2-methyl-1-{8-[2-(4-phenylpiperidin-4-yl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1*H*-benzimidazole (51 mg, 0.12 mmol), 5-fluoro-2-hydroxybenzoic acid (19 mg, 0.12 mmol) and HATU (47mg, 0.12 mmol), following the procedure outlined in example 5. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.67 (br, 1 H), 7.65 (d, J=7.0 Hz, 1 H), 7.41-7.37 (m, 2 H), 7.32-7.24(m, 4 H), 7.21-7.12 (m, 2 H), 7.05-7.01 (m, 1 H), 7.00-6.86 (m, 2 H), 4.61 (br, 1 H), 4.04-4.00 (m, 2 H), 3.38 (t, J=10.8 Hz, 2 H), 3.25 (br, 2 H), 2.55 (s, 3 H), 2.40-2.20 (m, 4 H), 1.94-1.83 (m, 10 H), 1.63-1.61 (m, 2 H). HRMS *m/z* $(M+H)^+$ calcd: 567.3135, obsd: 567.3130.

Example 471

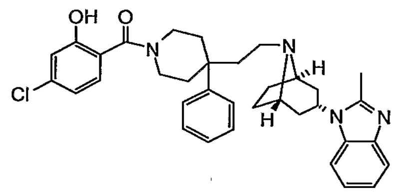
Preparation of 3-fluoro-2-[(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]phenol



3-Fluoro-2-[(4-{2-[(1*R*, 5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]phenol (53 mg, 78%) was obtained as a foam from 2-methyl-1-{8-[2-(4-phenyl piperidin-4-yl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1*H*-benzimidazole (51 mg, 0.12 mmol), 6-fluoro-2-hydroxy-benzoic acid (19 mg, 0.12 mmol) and HATU (47mg, 0.12 mmol), following the procedure outlined in example 5. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (d, J=8.6 Hz, 1 H), 7.44-7.36 (m, 2 H), 7.31-7.24(m, 3 H), 7.22-7.12 (m, 4 H), 6.97 (d, J=8.4 Hz, 1 H), 6.58 (t, J=9.0 Hz, 1 H), 4.64-4.55 (m, 1 H), 4.20 (br, 1 H), 3.59 (br, 1 H), 3.33 (br, 2 H), 2.54 (s, 3 H), 2.39-2.20 (m, 4 H), 1.99-1.81 (m, 10 H), 1.60 (d, J=7.1 Hz, 2 H). HRMS *m/z* $(M+H)^+$ calcd: 567.3135, obsd: 567.3117.

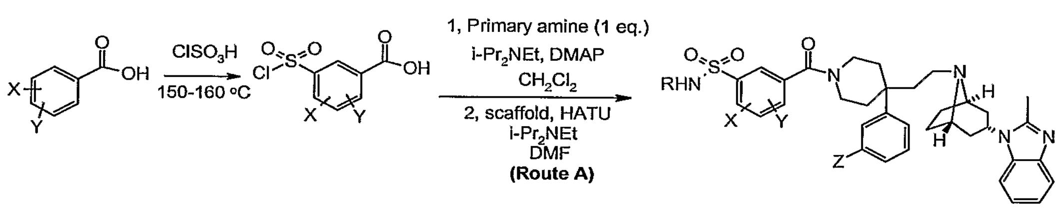
Example 472

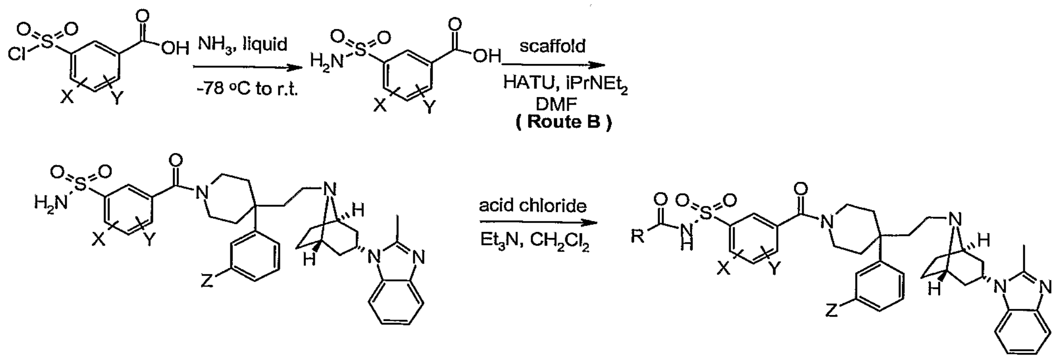
Preparation of 5-chloro-2-[(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]phenol

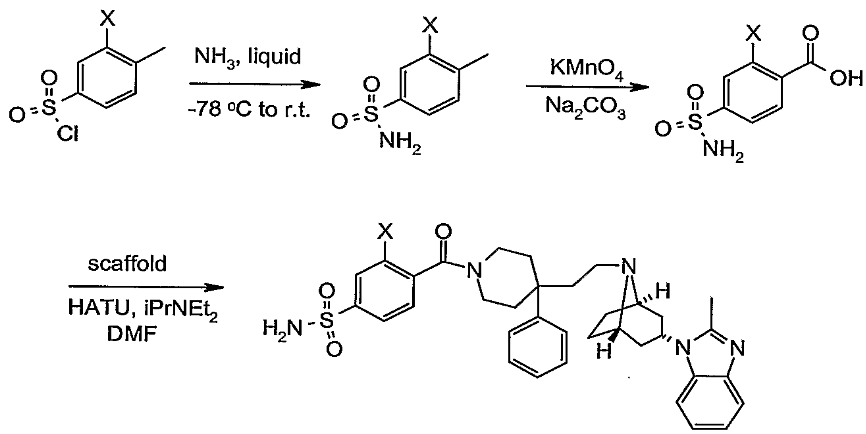


5-Chloro-2-[(4-{2-[(1R,5S)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]phenol (46 mg, 66%) was obtained as a foam from 2-methyl-1-{8-[2-(4-phenylpiperidin-4-yl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1*H*-benzimidazole (51 mg, 0.12 mmol), 4-chloro-2-hydroxybenzoic acid (21 mg, 0.12 mmol) and HATU (47mg, 0.12 mmol), following the procedure outlined in example 5. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (d, J=7.3 Hz, 1 H), 7.41-7.37 (m, 2 H), 7.32-7.24 (m, 4 H), 7.21-7.12 (m, 3 H), 7.02 (s, 1 H), 6.82 (d, J=6.4 Hz, 1 H), 4.60 (br, 1 H), 4.02-3.99 (m, 2 H), 3.41-3.35 (m, 2 H), 3.25 (br, 2 H), 2.56 (s, 3 H), 2.36-2.29 (m, 4 H), 1.94-1.84 (m, 10 H), 1.63-1.62 (m, 2 H). HRMS *m/z* $(M+H)^+$ calcd: 583.2840, obsd: 583.2839.

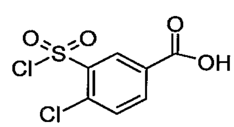
Preparation of meta- and para- N-subsutituted sulfonamides



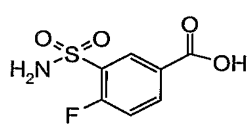




4-Chloro-3-(chlorosulfonyl)benzoic acid has been synthesized as described elsewhere in this application (Method G).

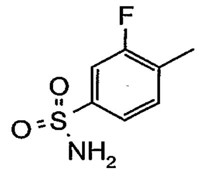


3-(Aminosulfonyl)-4-fluorobenzoic acid has been synthesized according to as Method G detailed elsewhere in this application.



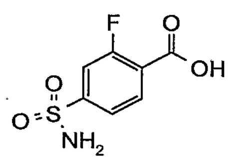
2,6-Difluoro-3-(aminosulfonyl)benzoic acid, 2,6-dichloro-3-(aminosulfonyl)benzoic acid, 3,4-difluoro-5-(aminosulfonyl)benzoic acid and 2,6-methyl-3-(aminosulfonyl)benzoic acid were prepared with the similar procedure as above.

Preparation of 3-fluoro-4-methylbenzenesulfonamide



To ~20 mL of liquid ammonia at -78°C was added 2.1g (10 mmol) of 3-fluoro-4-methyl benzenesulfonyl chloride. The excess ammonia was then naturally evaporated to dryness overnight at room temperature. The crude sulfonamide was partitioned methylene chloride (100mL) and water (100 mL). The aqueous phase was further extracted with methylene chloride. The combined organic extracts were dried over anhydrous sodium sulfate. Evaporation of the solvents afforded 1.9 g of 3-fluoro-4-methylbenzenesulfonamide as a solid.

Preparation of 4-(aminosulfonyl)-2-fluorobenzoic acid

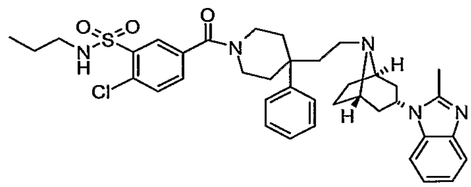


To a stirred solution of 3-fluoro-4-methyl-benzenesulfonamide (prepared above) in 50 mL of water was added sodium carbonate (0.53g, 5 mmol) and potassium permanganate (3.16g, 20 mmol) portionwise over three hours at 50~60 °C. The resulting mixture was stirred for further 8 hours at this temperature before 0.2 mL of formic acid was added to quench the excess of potassium permanganate. The mixture was then filtered through celite while it was still hot and further washed with the hot water. The filtrate was concentrated to ~30 mL and adjusted to pH 9~10. The filtration was applied again to remove non-oxidized starting material. The final filtrate was acidified with HCl (conc.) to ~ pH 1 and 4-(aminosulfonyl)-2-fluorobenzoic acid was precipitated and collected by filtration as white solid (1.10g, 50%).

The corresponding 4-(aminosulfonyl)-2-chlorobenzoic acid was prepared by the similar procedures.

Exmple 473

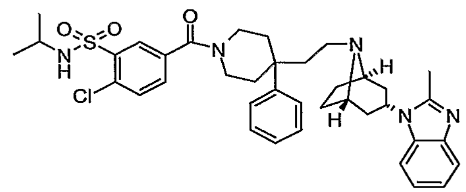
Preparation of 2-chloro-5-[(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]-N-propylbenzenesulfonamide



To a stirred solution of 4-chloro-3-(chlorosulfonyl)benzoic acid (25.4 mg, 0.1 mmol) in dichloromethane (3 mL) was added propylamine (9 μL, 0.11 mmol), *N,N*-diisopropylethylamine (39mg, 0.3 mmol) and 4-*N,N*-dimethylaminopyridine (2 mg, 0.016 mmol). After the resultant mixture was stirred overnight, a solution of 2-methyl-1-{(1*R*,5*S*)-8-[2-(4-phenyl piperidin-4-yl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1*H*-benzimidazole dihydrochloride (50 mg, 0.1 mmol) in *N,N*-dimethylforamide (3 mL) was added and followed by addition of *N, N*-diisopropylethylamine (39mg, 0.3 mmol) and HATU (38 mg. 0.1 mmol). The reaction mixture was stirred for further 4 hours before it was quenched with saturated sodium bicarbonate solution and extracted with dichloromethane. The combined organic extracts were dried over anhydrous sodium sulfate. After evaporation of solvents, the residue was purified by flash chromatography, eluting with a gradient of 0~8% methanol in ethyl acetate to afford 2-chloro-5-[(4-{2-[(*1R,5S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]-*N*-propylbenzenesulfonamide as solid (30 mg, 43%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (s, 1 H), 7.65 (d, J=8.4 Hz, 1 H), 7.65 (s, 2 H), 7.38 (t, J=7.5 Hz, 2 H), 7.30-7.23 (m, 4 H), 7.19-7.12 (m, 2 H), 5.10 (t, J=6.0 Hz, 1 H), 4.64-4.59 (m, 1 H), 4.19 (br, 1 H), 3.48 (br, 1 H), 3.34-3.35 (m, 4 H), 2.90 (q, J=6.3 Hz, 2 H), 2.57 (s, 3 H), 2.42-2.34 (m, 3 H), 2.20 (br, 1 H), 1.94-1.78 (m, 10 H), 1.62 (d, J=6.4 Hz, 2 H), 1.54-1.45 (m, 2 H), 0.88 (t, J=7.5 Hz, 3 H). HRMS *m/z* $(M+H)^+$ calcd: 688.3088, obsd: 688.3063.

Example 474

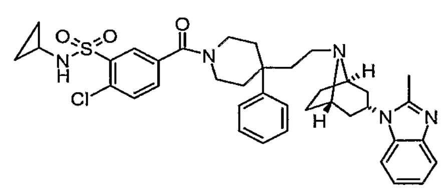
Preparation of 2-chloro-N-isopropyl-5-[(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1] oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]benzene sulfonamide



2-Chloro-*N*-isopropyl-5-[(4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]benzene sulfonamide (10 mg, 15%) was obtained as solid from 4-chloro-3-(chlorosulfonyl)benzoic acid (25.4 mg, 0.1 mmol), 2-methyl-1-{(1*R*,5*S*)-8-[2-(4-phenylpiperidin-4-yl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1*H*-benzimidazole dihydrochloride (50 mg, 0.1 mmol) and isopropylamine (9.4 μL, 0.11 mmol) following the procedure outlined in example 473. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.11 (s, 1 H), 7.67 (d, J=7.0 Hz, 1 H), 7.57 (s, 2 H), 7.42-7.37 (m, 2 H), 7.30-7.20 (m, 4 H), 7.18-7.12 (m, 2 H), 4.89 (d, J=7.5 Hz, 1 H), 4.64-4.59 (m, 1 H), 4.18 (br, 1 H), 3.49-3.29 (m, 6 H), 2.58 (s, 3 H), 2.38-2.16 (m, 4 H), 1.95-1.88 (m, 10 H), 1.65-1.63 (m, 2 H), 1.10 (d, J=6.5 Hz, 6 H). HRMS *m/z* $(M+H)^+$ calcd: 688.3088, obsd: 688.3093.

Example 475

Preparation of 2-chloro-N-cyclopropyl-5-[(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]benzenesulfonamide

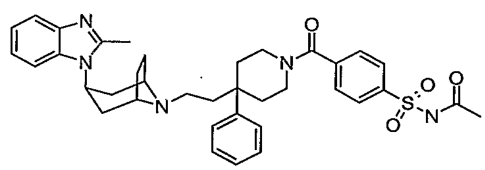


2-Chloro-*N*-cyclopropyl-5-[(4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]benzene sulfonamide (15 mg, 22%) was obtained as solid from 4-

chloro-3-(chlorosulfonyl)benzoic acid (25.4 mg, 0.1 mmol), 2-methyl-1-{(1*R*,5*S*)-8-[2-(4-phenylpiperidin-4-yl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1*H*-benzimidazole dihydrochloride (50 mg, 0.1 mmole), cyclopropylamine (7.6 μL, 0.11 mmol) and HATU (38 mg, 0.1 mmol) following the procedure outlined in example 473. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (s, 1 H), 7.66 (d, J=7.0 Hz, 1 H), 7.59 (s, 2 H), 7.41-7.37 (m, 2 H), 7.30-7.20 (m, 4 H), 7.18-7.13 (m, 2 H), 5.46 (s, 1 H), 4.65-4.60 (m, 1 H), 4.19 (br, 1 H), 3.50 (br, 1 H), 3.35-3.26 (m, 4 H), 2.57 (s, 3 H), 2.43-2.35 (m, 3 H), 2.19 (br, 2 H), 1.94-1.78 (m, 10 H), 1.63 (d, J=7.9 Hz, 2 H), 0.68-0.58 (m, 4 H). HRMS *m/z* $(M+H)^+$ calcd: 686.2932, obsd: 686.2935.

Example 476

Preparation of N-acetyl-4-[(4-{2-[3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]benzene-sulfonamide

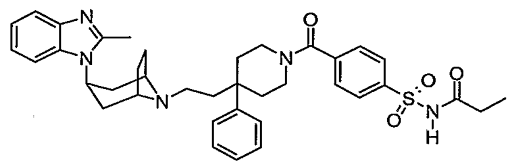


To a precooled (0 °C) solution of 4-[(4-{2-[3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]-benzene-sulfonamide (20 mg, 0.033 mmol) in dichloromethane (2 mL) was added acetyl bromide (4.2 mg, 0.034 mmol) and *N,N*-diisopropylethyl amine (12 μL, 0.66 mmol). The resulting mixture was stirred overnight at ambient temperature. After evaporation of the solvent, the crude product was purified by flash chromatography on silical gel, eluting with a gradient of 15-30% methanol in ethyl acetate to afford *N*-acetyl-4-[(4-{2-[3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]benzene-sulfonamide as amorphous solid (14 mg, 66%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.83 (d, J=8.1 Hz, 2 H), 7.48-7.46 (m, 3 H), 7.37-7.33 (m, 5 H), 7.21 (br, 1 H), 7.13 –7.05 (m, 2 H), 4.51 (t, J=8.1, 1 H), 3.88 (br, 1 H), 3.67-3.15 (m, 6 H), 2.42 (s, 3 H), 2.37-2.30 (m, 2 H), 2.11-2.07 (br, 2 H),

1.96-1.72 (m, 13 H), 1.59 (d, J=7.4, 2 H). HRMS *m/z* $(M+H)^+$ calcd: 654.3114, obsd: 654.3095.

Example 477

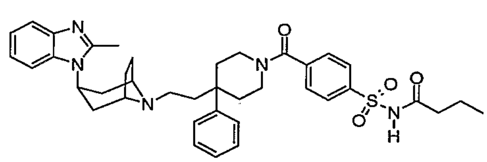
Preparation of 4-[(4-{2-[3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo-[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]-N-propionylbenzene-sulfonamide



4-[(4-{2-[3-(2-Methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]-*N*-propionylbenzenesulfonamide (13 mg, 59%) was obtained from 4-[(4-{2-[3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]-benzenesulfonamide (20 mg, 0.033 mmol) and propionyl chloride as amorphous solid by the similar procedure outlined in example 476. ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.87 (d, J=8.0 Hz, 2 H), 7.53-7.42 (m, 3 H), 7.39-7.35 (m, 5 H), 7.25-7.21 (m, 1 H), 7.15-7.07 (m, 2 H), 4.66 (br, 1 H), 3.90 (br, 1 H), 3.19-3.16 (m, 5 H), 2.45 (s, 3 H), 2.42-2.35 (m, 2 H), 2.22-2.09 (m, 5 H), 1.98-1.78 (m, 10 H), 1.66 (d, J=7.3 Hz, 2 H), 1,17 (t, J=7.2 Hz, 3 H). HRMS *m/z* $(M+H)^+$ calcd: 668.3271, obsd: 668.3256.

Example 478

Preparation of N-butyryl-4-[(4-{2-[3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]benzene-sulfonamide

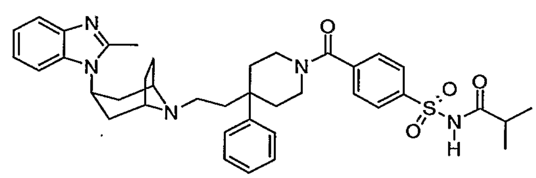


N-butyryl-4-[(4-{2-[3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo-[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]benzenesulfonamide (15

mg, 68%) was obtained from 4-[(4-{2-[3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]-benzenesulfonamide (20 mg, 0.033 mmol) and butyryl chloride by the similar procedure outlined in example 476. ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.87 (d, J=8.1 Hz, 2 H), 7.52-7.4 (m, 3 H), 7.39-7.35 (m, 5 H), 7.25-7.21 (m, 1 H), 7.15-7.07 (m, 2 H), 4.69 (br, 1 H), 3.89 (br, 1 H), 3.16 (m, 5 H), 2.45 (s, 3 H), 2.42-2.35 (m, 2 H), 2.23-2.05 (m, 5 H), 1.98-1.78 (m, 10 H), 1.68-1.66 (m, 2 H), 1.40 (q, J=7.3 Hz, 2 H),17 (t, J=7.3 Hz, 3 H). HRMS *m/z* (M+H)$^+$ calcd: 682.3427, obsd: 682.3426.

Example 479

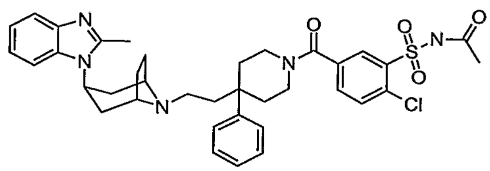
Preparation of N-isobutyryl-4-[(4-{2-[3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]benzene-sulfonamide



N-isobutyryl-4-[(4-{2-[3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo-[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]benzenesulfonamide (14 mg, 64%) was obtained from 4-[(4-{2-[3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]-benzenesulfonamide (20 mg, 0.033 mmol) and isobutyryl chloride by the similar procedure outlined in example 476. ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.84 (d, J=8.2 Hz, 2 H), 7.50-7.47 (m, 3 H), 7.41-7.35 (m, 5 H), 7.25-7.21 (m, 1 H), 7.15-7.07 (m, 2 H), 4.60 (br, 1 H), 3.90 (br, 1H), 3.75-3.16 (m, 5 H), 2.45 (s, 3 H), 2.42-2.23 (m, 3 H), 2.13-2.08(m, 2 H), 1.98-1.78 (m, 11 H), 1.65-1.62 (m, 2 H), 0.92 (d, J=6.8 Hz, 6 H). HRMS *m/z* (M+H)$^+$ calcd: 682.3427, obsd: 682.3408.

Example 480

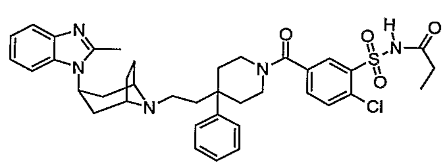
Preparation of N-acetyl-2-chloro-5-[(4-{2-[3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]benzene-sulfonamide



N-acetyl-2-chloro-5-[(4-{2-[3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl] benzene-sulfonamide (21.8 mg, quant.) was obtained as amorphous solid from 2-chloro-5-[(4-{2-[3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl] benzenesulfonamide and acetyl bromide following the procedure outlined in example 476. ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.85-7.50 (m, 3 H), 7.49 (d, J=8.5 Hz, 1 H), 7.41-7.35 (m, 5 H), 7.25-7.21 (m, 1 H), 7.15-7.09 (m, 2 H), 4.54 (br, 1 H), 3.96 (br, 1 H), 3.42-3.29 (m, 5 H), 3.06-3.03 (m, 1 H), 2.45-2.36 (m, 5 H), 2.17-2.07 (m, 2 H), 1.98-1.75 (m, 10 H), 1.71-1.70 (m, 3 H), 1.63-1.61 (m, 2 H). HRMS *m/z* $(M+H)^+$ calcd: 688.2724, obsd: 688.2745.

Example 481

Preparation of 2-chloro-5-[(4-{2-[3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]-N-propionyl benzenesulfonamide

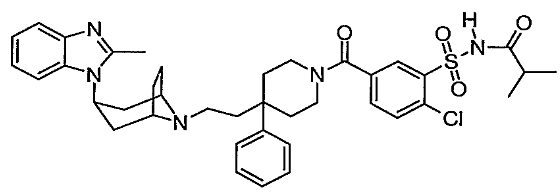


2-Chloro-5-[(4-{2-[3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo-[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]-*N*-propionylbenzene-sulfonamide(16 mg, 73%) was obtained as amorphous solid from 2-chloro-5-[(4-{2-[3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenyl piperidin-1-yl)carbonyl] benzenesulfonamide and propionyl chloride

following the procedure outlined in example 476. ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.81-7.56 (m, 3 H), 7.49 (d, J=8.4 Hz, 1 H), 7.39-7.26 (m, 5 H), 7.24-7.08 (m, 3 H), 4.80 (br, 1 H), 3.99-3.93 (m, 1 H), 3.58-3.38 (m, 5 H), 3.11-2.99 (m, 1 H), 2.47 (m, 4 H), 2.22-1.72 (m, 17 H), 0.89-0.81 (m, 3 H). HRMS *m/z* $(M+H)^+$ calcd: 702.2881, obsd: 702.2885.

Example 482

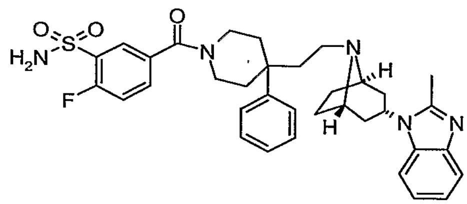
Preparation of 2-chloro-N-isobutyryl-5-[(4-{2-[3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl] benzenesulfonamide



2-Chloro-*N*-isobutyryl-5-[(4-{2-[3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl] benzene-sulfonamide (19 mg, 80%) was obtained as amorphous solid from 2-chloro-5-[(4-{2-[3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]benzenesulfonamide and isobutyryl chloride following the procedure outlined in example 476. ^{1}H NMR (300 MHz, DMSO-d_6, 100 °C) δ 7.85-7.76 (m, 2 H), 7.60-7.50 (m, 2 H), 7.42-7.28 (m, 5 H), 7.26 (m, 1 H), 7.18-7.12 (m, 2 H), 4.76 (br, 1 H), 3.36-3.08 (m, 7 H), 2.53-2.27 (m, 7 H), 204-1.82 (m, 10 H), 1.69 (d, J=7.6 Hz, 2 H), 0.95 (d, J=6.6 Hz, 6 H). HRMS *m/z* $(M+H)^+$ calcd: 716.3037, obsd: 716.3013.

Example 483

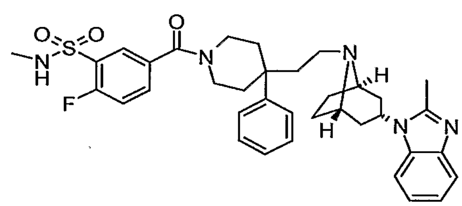
Preparation of 2-fluoro-5-[(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]benzene-sulfonamide



2-Fluoro-5-[(4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]benzenesulfonamide (20 mg, 32%) was obtained as solid from 3-(aminosulfonyl)-4-fluorobenzoic acid (22 mg, 0.1 mmol), 2-methyl-1-{(1*R*,5*S*)-8-[2-(4-phenylpiperidin-4-yl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1*H*-benzimidazole dihydrochloride (50 mg, 0.1 mmol) and HATU (38 mg, 0.1 mmol) following the procedure outlined in example 5. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93-7.91(m, 1 H), 7.64-7.58 (m, 2 H), 7.40-7.36 (m, 2 H), 7.30-7.21 (m, 5 H), 7.19-7.12 (m, 2 H), 5.61 (br, 1 H), 4.66-4.56 (m, 1 H), 4.20 (br, 1 H), 3.56 (br, 1 H), 3.26 (m, 4 H), 2.57 (s, 3 H), 2.42-2.34 (m, 4 H), 2.20 (br, 2 H), 1.99-1.83 (m, 9 H), 1.62 (m, 2 H). HRMS *m/z* $(M+H)^+$ calcd: 630.2914, obsd: 630.2925.

Example 484

Preparation of 2-fluoro-N-methyl-5-[(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]benzene-sulfonamide

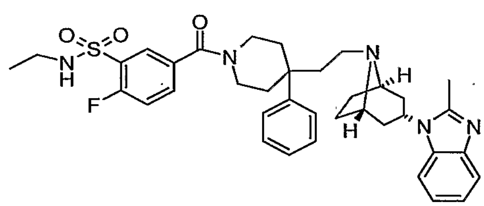


2-Fluoro-*N*-methyl-5-[(4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]benzene

sulfonamide (53.8mg, 56%) was obtained as solid from 4-fluoro-3-(chlorosulfonyl)benzoic acid (48 mg, 0.2 mmol), 2-methyl-1-{(1*R*,5*S*)-8-[2-(4-phenylpiperidin-4-yl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1*H*-benzimidazole dihydrochloride (76 mg, 0.15 mmol) and methylamine (0.10 mL, 2.0 M in THF) following the procedure outlined in example 473. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92-7.90(m, 1 H), 7.65-7.61 (m, 2 H), 7.40-7.36 (m, 2 H), 7.30-7.22 (m, 5 H), 7.18-7.12 (m, 2 H), 5.29 (d, J=4.9 Hz, 1 H), 4.63-4.58 (m, 1 H), 4.18 (br, 1 H), 3.50 (br, 1 H), 3.32-3.25 (m, 4 H), 2.71 (d, J=4.1 Hz, 3 H), 2.56 (s, 3 H), 2.41-2.33 (m, 3 H), 2.16 (br, 2 H), 1.92-1.81 (m, 10 H), 1.64-1.58 (m, 2 H). HRMS *m/z* $(M+H)^+$ calcd: 644.3071, obsd: 644.3061.

Example 485

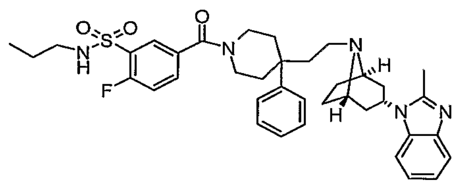
Preparation of N-ethyl-2-fluoro-5-[(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]benzene-sulfonamide



N-Ethyl-2-fluoro-5-[(4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]benzene sulfonamide (30.5 mg, 30%) was obtained as solid from 4-fluoro-3-(chlorosulfonyl)benzoic acid (48 mg, 0.2 mmol), 2-methyl-1-{(1*R*,5*S*)-8-[2-(4-phenylpiperidin-4-yl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1*H*-benzimidazole dihydrochloride (76 mg, 0.15 mmol) and ethylamine (0.10 mL, 2.0 M in THF) following the procedure outlined in example 473. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93-7.90(m, 1 H), 7.66-7.61 (m, 2 H), 7.40-7.36 (m, 2 H), 7.30-7.22 (m, 5 H), 7.19-7.12 (m, 2 H), 4.94 (t, J=6.1 Hz, 1 H), 4.65-4.57 (m, 1 H), 4.17 (br, 1 H), 3.50 (br, 1 H), 3.26 (br, 4 H), 3.11-3.04 (m, 2 H), 2.56 (s, 3 H), 2.42-2.34 (m, 3 H), 2.20-2.17 (m, 1 H), 1.94-1.82 (m, 10 H), 1.64 (d, J=6.4 Hz, 2 H), 1.13 (t, J=7.1 Hz, 3 H). HRMS *m/z* $(M+H)^+$ calcd: 658.3227, obsd: 658.3237.

Example 486

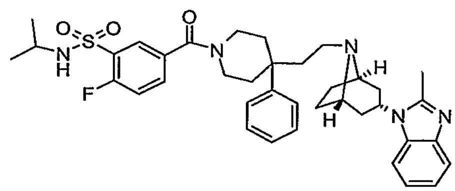
Preparation of 2-fluoro-5-[(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]-N-propylbenzenesulfonamide



2-Fluoro-5-[(4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]-*N*-propylbenzene sulfonamide (41.8 mg, 41%) was obtained as solid from 4-fluoro-3-(chlorosulfonyl)benzoic acid (48 mg, 0.2 mmol), 2-methyl-1-{(1*R*,5*S*)-8-[2-(4-phenylpiperidin-4-yl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1*H*-benzimidazole dihydrochloride (76 mg, 0.15 mmol) and propylamine (16.5 μL, 0.2mmol) following the procedure outlined in example 473. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92-7.90(m, 1 H), 7.66-7.61 (m, 2 H), 7.40-7.36 (m, 2 H), 7.30-7.22 (m, 5 H), 7.19-7.12 (m, 2 H), 5.03 (t, J=6.0 Hz, 1 H), 4.64-4.56 (m, 1 H), 4.18 (br, 1 H), 3.50 (br, 1 H), 3.33-3.25 (m, 4 H), 2.97 (q, J=6.8Hz, 2 H), 2.56 (s, 3 H), 2.42-2.34 (m, 3 H), 2.19 (br, 1 H), 2.10 (s, 1 H), 1.93-1.82 (m, 10 H), 1.62 (d, J=6.4 Hz, 2 H), 1.55-1.46 (m, 2 H), 0.88(t, J=7.5 Hz, 3 H). HRMS *m/z* $(M+H)^+$ calcd: 672.3384, obsd: 672.3380.

Example 487

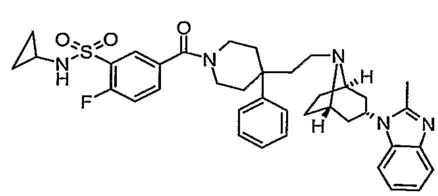
Preparation of 2-fluoro-N-isopropyl-5-[(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1] oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]benzene sulfonamide



2-Fluoro-*N*-isopropyl-5-[(4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]benzene sulfonamide (35.6mg, 35%) was obtained as solid from 4-fluoro-3-(chlorosulfonyl)benzoic acid (48 mg, 0.2 mmol), 2-methyl-1-{(1*R*,5*S*)-8-[2-(4-phenylpiperidin-4-yl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1*H*-benzimidazole dihydrochloride (76 mg, 0.15 mmol) and isopropylamine (17 μL, 0.2mmol) following the procedure outlined in example 473. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94-7.91 (m, 1 H), 7.67-7.61 (m, 2 H), 7.40-7.37 (m, 2 H), 7.30-7.22 (m, 5 H), 7.19-7.12 (m, 2 H), 4.75 (d, J=7.5 Hz, 1 H), 4.65-4.60 (m, 1 H), 4.19 (br, 1 H), 3.56-3.48 (m, 2 H), 3.33-3.26 (br, 4 H), 2.57 (s, 3 H), 2.41-2.34 (m, 3 H), 2.19-2.17 (br, 1 H), 1.94-1.82 (m, 11 H), 1.62 (d, J=7.9 Hz, 2 H), 1.11 (d, J=6.4 Hz, 6 H). HRMS *m/z* $(M+H)^+$ calcd: 672.3384, obsd: 672.3398.

Example 488

Preparation of N-cyclopropyl-2-fluoro-5-[(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]benzenesulfonamide

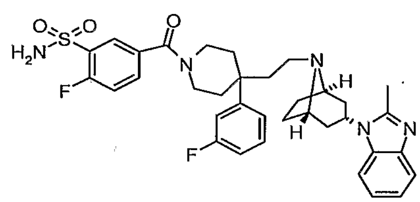


N-Cyclopropyl-2-fluoro-5-[(4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-

yl)carbonyl]benzene sulfonamide (43.0 mg, 43%) was obtained as solid from 4-fluoro-3-(chlorosulfonyl)benzoic acid (48 mg, 0.2 mmol), cyclopropyl amine (14 μL, 0.2mmol) and 2-methyl-1-{(1*R*,5*S*)-8-[2-(4-phenylpiperidin-4-yl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1*H*-benzimidazole dihydrochloride (76 mg, 0.15 mmol) following the procedure outlined in example 473. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97-7.95 (m, 1 H), 7.69-7.64 (m, 2 H), 7.40-7.36 (m, 2 H), 7.30-7.23 (m, 5 H), 7.19-7.12 (m, 2 H), 5.47 (s, 1 H), 4.64-4.56 (m, 1 H), 4.19 (br, 1 H), 3.51 (br, 1 H), 3.33-3.26 (m, 4 H), 2.56 (s, 3 H), 2.41-2.28 (m, 3 H), 2.27-2.17 (m, 2 H), 1.99-1.82 (m, 12 H), 1.62 (d, J=7.9 Hz, 2 H), 0.68-0.60 (m, 4 H). HRMS *m/z* $(M+H)^+$ calcd: 670.3227, obsd: 670.3213.

Example 489

Preparation of 2-fluoro-5-[(4-(3-fluorophenyl)-4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)carbonyl]benzenesulfonamide

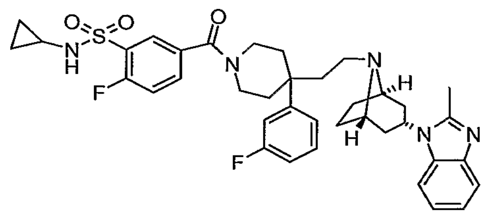


2-Fluoro-5-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)carbonyl]benzenesulfonamide (35 mg, 54%) was obtained as solid from 3-(aminosulfonyl)-4-fluorobenzoic acid (22 mg, 0.1 mmol), 1-((1*R*,5*S*)-8-{2-[4-(3-fluorophenyl)piperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1*H*-benzimidazole dihydrochloride (52 mg, 0.1 mmol) and HATU (38mg, 0.10mmol) following the procedure outlined in example 473. ^{1}H NMR (400 MHz, $CDCl_3$), δ 7.96 (dd, J=6.8 Hz, 2.1 Hz, 1 H), 7.63-7.61 (m, 1 H), 7.59-7.55 (m, 1 H), 7.37-7.32 (m, 1 H), 7.29-7.20 (m, 2 H), 7.18-7.10 (m, 2 H), 7.06 (d, J=8.0 Hz, 1 H), 6.99-6.90 (m, 2 H), 6.04 (br, 2 H), 4.66 (t, J=8.8 Hz, 1 H), 4.14-4.08 (m, 1 H), 3.50 (br, 1 H), 3.9 (br, 4 H), 2.52 (s, 3 H), 2.44-2.36 (m, 2

H), 2.24 (br, 1 H), 2.09 (br, 1 H), 1.96-1.84 (m, 10 H), 1.65 (d, J=7.8 Hz, 2 H). HRMS *m/z* $(M+H)^+$ calcd: 648.2820, obsd: 648.2822.

Example 490

Preparation of N-cyclopropyl-2-fluoro-5-[(4-(3-fluorophenyl)-4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)carbonyl]benzenesulfonamide

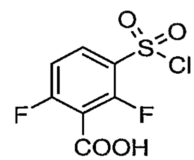


N-Cyclopropyl-2-fluoro-5-[(4-(3-fluoro phenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)carbonyl]benzenesulfonamide (22 mg, 32%) was obtained as solid from 4-fluoro-3-(chlorosulfonyl) benzoic acid (48 mg, 0.2 mmol), cyclopropyl amine (14 μL, 0.2mmol) and 1-((1*R*,5*S*)-8-{2-[4-(3-fluorophenyl) piperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1*H*-benzimidazole dihydrochloride (52 mg, 0.1 mmol) following the procedure outlined in example 473. ^1H NMR (400 MHz, $CDCl_3$), δ 7.96 (dd, J=6.7 Hz, 2.2 Hz, 1 H), 7.69-7.65 (m, 2 H), 7.39-7.33 (m, 1 H), 7.30-7.25 (m, 2 H), 7.19-7.12 (m, 2 H), 7.07 (d, J=8.0 Hz, 1 H), 7.01-6.94 (m, 2 H), 5.39 (s, 1 H), 4.66 (br, 1 H), 4.16 (br, 1 H), 3.54 (br, 1 H), 3.48-3.28 (m, 4 H), 2.58 (s, 3 H), 2.44-2.37 (m, 2 H), 2.29-2.20 (m, 2 H), 2.13 (br, 1 H), 1.97-1.81 (m, 10 H), 1.66 (d, J=7.9 Hz, 2 H), 0.68-0.61 (m, 4 H). HRMS *m/z* $(M+H)^+$ calcd: 688.3133, obsd: 688.3146.

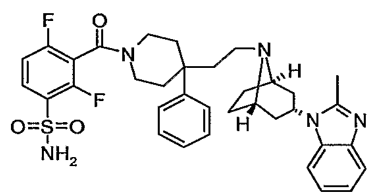
Example 491

2,4-difluoro-3-[(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]benzenesulfonamide

Preparation of 3-(chlorosulfonyl)-2,6-difluorobenzoic acid



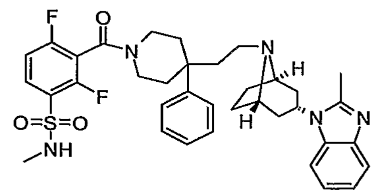
3-(Chlorosulfonyl)-2,6-difluorobenzoic acid (8.6 g, 67%) was obtained as solid from 2,6-difluorobenzic acid (8 g, 50 mmol), following the procedure outlined in the preparation of 4-chloro-3-(chlorosulfonyl)benzoic acid.



2,4-Difluoro-3-[(4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]benzene sulfonamide (22mg, 34%) was obtained as solid from 3-(aminosulfonyl)-2,6-difluorobenzoic acid (24 mg, 0.1 mmol), 2-methyl-1-{(1*R*,5*S*)-8-[2-(4-phenylpiperidin-4-yl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1*H*-benzimidazole dihydrochloride (50 mg, 0.10 mmol) and HATU (38mg, 0.1 mmol) following the procedure outlined in example 473. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00-7.89 (m, 1 H), 7.64 (d, J=7.7 Hz, 1 H), 7.40-7.34 (m, 2 H), 7.30-7.24 (m, 4 H), 7.19-7.12 (m, 2 H), 7.07-6.97 (m, 1 H), 5.6 (br, 2 H), 4.66-4.55 (m, 1 H), 4.29-4.24 (m, 1 H), 3.58-3.31 (m, 2 H), 3.25- 3.05 (m, 3 H), 2.54 (s, 3 H), 2.49-2.20 (m, 4 H), 1.99-1.76 (m, 10 H), 1.62 (d, J=7.7 Hz, 2 H). HRMS *m/z* $(M+H)^+$ calcd: 648.2820, obsd: 648.2834.

Example 492

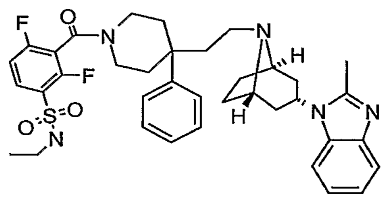
Preparation of 2,4-difluoro-N-methyl-3-[(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1] oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl] benzenesulfonamide



2,4-Difluoro-*N*-methyl-3-[(4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]benzene sulfonamide (90 mg, 40%) was obtained as solid from 3-(chlorosulfonyl)-2,6-difluorobenzoic acid (105 mg, 0.4 mmol), 2-methyl-1-{(1*R*,5*S*)-8-[2-(4-phenyl piperidin-4-yl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1*H*-benzimidazole dihydrochloride (177 mg, 0.35 mmol) and methylamine (230 μL, 2.0 M in THF) following the procedure outlined in example 473. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98-7.92 (m, 1 H), 7.67-7.65 (d, 1 H), 7.41-7.37 (m, 2 H), 7.30-7.28 (m, 4 H), 7.21-7.03 (m, 3 H), 4.84(m, ½ H, rotamer), 4.75-4.71 (m, ½ H, rotamer), 4.66-4.58 (m, 1 H), 3.41- 3.20 (m, 5 H), 2.74 (d, J=5.1 Hz, 3/2 H, rotamer), 2.69 (d, J=5.1 Hz, 3/2 H, rotamer), 2.57 (s, 3/2 H, rotamer), 2.56 (s, 3/2 H, rotamer), 2.41-2.37 (m, 3 H), 2.26-2.23 (m, 2 H), 1.99-1.77 (m, 9 H), 1.69-1.62 (m, 4 H). HRMS *m/z* $(M+H)^+$ calcd: 662.2976, obsd: 662.2982.

Example 493

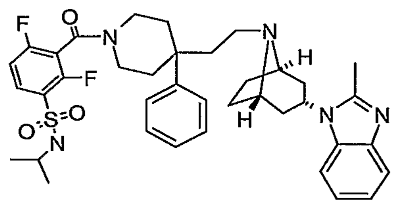
Preparation of N-ethyl-2, 4-difluoro-3-[(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]benzenesulfonamide



N-Ethyl-2, 4-difluoro-3-[(4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]benzene sulfonamide (92 mg, 45%) was obtained as solid from 3-(chlorosulfonyl)-2,6-difluorobenzoic acid (105 mg, 0.4 mmol), 2-methyl-1-{(1*R*,5*S*)-8-[2-(4-phenylpiperidin-4-yl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1*H*-benzimidazole dihydrochloride (150 mg, 0.30 mmol) and ethylamine (230 µL, 2.0 M in THF) following the procedure outlined in example 473. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01-7.92 (m, 1 H), 7.70 (m, ½ H, rotamer), 7.66 (d, J=7.1 Hz, 1 H), 7.54-7.52 (m, ½ H, rotamer), 7.41-7.32 (m, 2 H), 7.30-7.25 (m, 4 H), 7.20-7.13 (m, 2 H), 7.11-7.02 (m, 1 H), 4.90-4.59 (m, 2 H), 4.35-4.27 (m, 2 H), 3.42- 3.20 (m, 5 H), 3.18-2.96 (m, 2 H), 2.57 (s, 3/2 H, rotamer), 2.56 (s, 3/2 H, rotamer), 2.42-2.35 (m, 3 H), 2.26-2.23 (m, 1 H), 1.99-1.76 (m, 9 H), 1.68-1.62 (m, 2 H), 0.89-0.82 (m, 3 H). HRMS *m/z* (M+H)$^+$ calcd: 676.3133, obsd: 676.3154.

Example 494

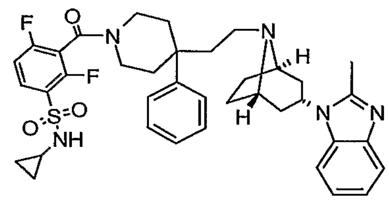
Preparation of 2,4-difluoro-N-isopropyl-3-[(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]benzenesulfonamide



2,4-Difluoro-*N*-isopropyl-3-[(4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]benzene sulfonamide (100 mg, 41%) was obtained as solid from 3-(chlorosulfonyl)-2,6-difluorobenzoic acid (105 mg, 0.4 mmol), 2-methyl-1-{(1*R*,5*S*)-8-[2-(4-phenylpiperidin-4-yl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1*H*-benzimidazole dihydrochloride (177 mg, 0.35 mmol) and isopropylamine (40 μL, 0.45 mmol) following the procedure outlined in example 473. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01-7.93 (m, 1 H), 7.66 (d, J=7.5 Hz, 1 H), 7.41-7.37 (m, 2 H), 7.30-7.25 (m, 5 H), 7.20-7.14(m, 2 H), 7.12-7.01 (m, 1 H), 4.80-4.65 (m, 2 H), 4.29-4.23 (m, 1 H), 3.55-3.49 (m. 1H), 3.40- 3.18 (m, 5 H), 2.58 (s, 3/2 H, rotamer), 2.57 (s, 3/2 H, rotamer), 2.40 (br, 3 H), 2.24-2.23 (m, 1 H), 1.96-1.73 (m, 10 H), 1.67-1.65 (m, 2 H), 1.21-1.16 (m, 3 H), 1.10-1.04 (m, 3 H). HRMS *m/z* $(M+H)^+$ calcd: 690.3289, obsd: 690.3276.

Example 495

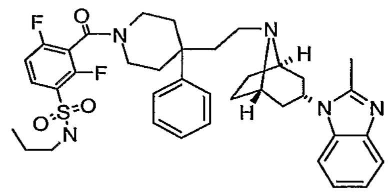
Preparation of N-cyclopropyl-2,4-difluoro-3-[(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]benzenesulfonamide



N-Cyclopropyl-2,4-difluoro-3-[(4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1] oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]benzene sulfonamide (110 mg, 48%) was obtained as solid from 3-(chlorosulfonyl)-2,6-difluorobenzoic acid (105 mg, 0.4 mmol), 2-methyl-1-{(1*R*,5*S*)-8-[2-(4-phenylpiperidin-4-yl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1*H*-benzimidazole dihydrochloride (150 mg, 0.30 mmol) and cyclopropylamine (32 μL, 0.45 mmol) following the procedure outlined in example 473. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02-7.97 (m, 1 H), 7.65 (d, J=7.2 Hz, 1 H), 7.41-7.37 (m, 2 H), 7.30-7.24 (m, 4 H), 7.20-7.04 (m, 2 H), 5,43 (s, ½ H, rotamer), 5.31 (s, ½ H, rotamer), 4.65-4.59 (m, 1 H), 4.30-4.27 (m, 1 H), 3.39-3.20 (m. 5H), 2.57 (s, 3/2 H, rotamer), 2.56 (s, 3/2 H, rotamer), 2.42-2.24 (m, 4H), 1.99-1.77 (m, 11 H), 1.65-1.60 (m, 2 H), 0.80-0.76 (m, 1 H), 0.75-0.55 (m, 3 H). HRMS *m/z* $(M+H)^+$ calcd: 688.3133, obsd: 688.3135.

Example 496

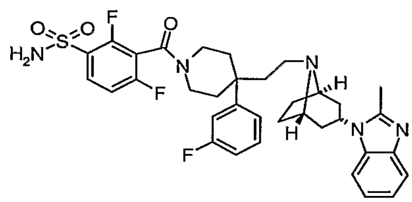
Preparation of 2,4-difluoro-3-[(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]-N-propylbenzenesulfonamide



2,4-Difluoro-3-[(4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]-*N*-propylbenzenesulfonamide (34.6mg, 34%) was obtained as solid from 3-(chlorosulfonyl)-2,6-difluorobenzoic acid (52 mg, 0.2 mmol), 2-methyl-1-{(1*R*,5*S*)-8-[2-(4-phenylpiperidin-4-yl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1*H*-benzimidazole dihydrochloride (76 mg, 0.15 mmol) and propylamine (16.5 μL, 0.2 mmol) following the procedure outlined in example 473. ^{1}H NMR (400 MHz, $CDCl_3$), δ 8.01-7.91 (m, 1 H), 7.65 (d, J=7.1 Hz, 1 H), 7.41-7.37 (m, 2 H), 7.30-7.28 (m, 4 H), 7.19-7.01 (m, 3 H), 4.96 (t, J=5.8 Hz, ½ H, rotamer), 4.87 (t, J=6.2 Hz, ½ H, rotamer), 4.65-4.58 (m, 1 H), 4.31-4.25 (m, 1 H), 3.40-3.23 (m, 5 H), 2.57 (s, 3/2 H, rotamer), 2.56 (s, 3/2 H, rotamer), 2.39-2.37 (m, 3 H), 2.25-2.22 (m, 1 H), 1.97-1.76 (m, 10 H), 1.65-1.63 (m, 2 H), 1.56-1.47 (m, 2 H), 0.92-0.85 (m, 3 H). HRMS *m/z* $(M+H)^+$ calcd: 690.3289, obsd: 690.3301.

Example 497

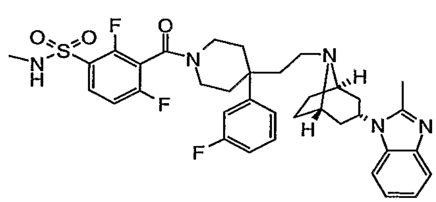
Preparation of 2,4-difluoro-3-[(4-(3-fluorophenyl)-4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)carbonyl]benzenesulfonamide



2,4-Difluoro-3-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)carbonyl]benzenesulfonamide (10 mg, 15%) was obtained as solid from 3-(aminosulfonyl)-2,6-difluorobenzoic acid (24 mg, 0.1 mmol), 1-((1*R*,5*S*)-8-{2-[4-(3-fluorophenyl)piperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1*H*-benzimidazole dihydrochloride (52mg, 0.10 mmol) and HATU (38mg, 0.1 mmol) following the procedure outlined in example 473. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01-7.92 (m, 1 H), 7.65 (d, J=7.7 Hz, 1 H), 7.39-7.34 (m, 1 H), 7.30-7.26 (m, 1 H), 7.21-7.13 (m, 2 H), 7.08-6.95 (m, 4 H), 5.35 (br, 2 H), 4.64-4.60 (m, 1 H), 4.26-4.23 (m, 1 H), 3.48-3.20 (m, 5 H), 2.56 (s, 3 H), 2.46-2.17 (m, 4 H), 1.99-1.64 (m, 12 H). HRMS *m/z* $(M+H)^+$ calcd: 666.2725, obsd: 666.2746.

Example 498

Preparation of 2,4-difluoro-3-[(4-(3-fluorophenyl)-4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)carbonyl]-N-methylbenzenesulfonamide

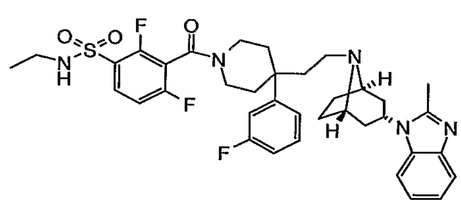


2,4-Difluoro-3-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)carbonyl]-*N*-methylbenzenesulfonamide (14 mg, 21%) was obtained as solid from 2,6-

difluoro-3-(chlorosulfonyl)benzoic acid (52 mg, 0.2 mmol), methylamine (120 µL, 2.0 M in THF) and 1-((1*R*,5*S*)-8-{2-[4-(3-fluorophenyl)piperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1*H*-benzimidazole dihydrochloride (52 mg, 0.1 mmol) following the procedure outlined in example 473. ^{1}H NMR (400 MHz, $CDCl_3$), δ 7.94 (q, J=8.0 Hz, 1 H), 7.65 (d, J=7.3 Hz, 1 H), 7.35 (q, J=8.0 Hz, 1 H), 7.29 (d, J=8.0 Hz, 1 H), 7.19-7.12 (m, 2 H), 7.09-7.02 (m, 2 H), 6.98-6.94 (m, 2 H), 4.99-4.86 (two sets of multiplets, 1 H, rotamers), 4.63-4.61 (m, 1 H), 4.27-4.23 (m, 1 H), 3.41-3.34 (m, 2 H), 3.25-3.18 (m, 3 H), 2.73 (d, J=5.0 Hz, 3/2 H, rotamer), 2.70 (d, J=4.9 Hz, 3/2 H, rotamer), 2.57 (s, 3/2 H, rotamer), 2.56 (s, 3/2 H, rotamer), 2.43-2.28 (m, 3 H), 2.22-2.17 (m, 1 H), 1.94-1.77 (m, 10 H), 1.66-1.63 (m, 2 H). HRMS *m/z* $(M+H)^+$ calcd: 680.2882, obsd: 680.2881.

Example 499

Preparation of N-ethyl-2,4-difluoro-3-[(4-(3-fluorophenyl)-4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)carbonyl]benzenesulfonamide

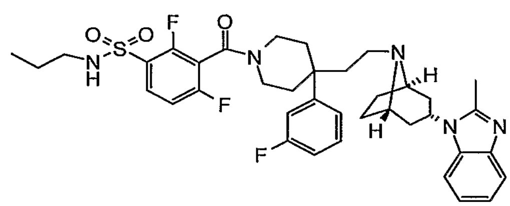


N-Ethyl-2,4-difluoro-3-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)carbonyl]benzenesulfonamide (16 mg, 23%) was obtained as solid from 2,6-difluoro-3-(chlorosulfonyl) benzoic acid (52 mg, 0.2 mmol), ethylamine (120 µL, 2.0 M in THF) and 1-((1*R*,5*S*)-8-{2-[4-(3-fluorophenyl) piperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1*H*-benzimidazole dihydrochloride (52 mg, 0.1 mmol) following the procedure outlined in example 473. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (q, J=8.0 Hz, 1 H), 7.66 (d, J=8.0 Hz, 1 H), 7.36 (q, J=8.0 Hz, 1 H), 7.30-7.28 (m, 1 H), 7.19-7.12 (m, 2 H), 7.09-7.04 (m, 2 H), 7.01-6.95 (m, 2 H), 4.93-4.84 (two sets of multiplets, 1

H, rotamers), 4.64 (br, 1 H), 4.27-4.24 (m, 1 H), 3.41-3.37 (m, 2 H), 3.26-3.25 (m, 3 H), 3.22-2.95 (m, 2 H), 2.58 (s, 3/2 H, rotamer), 2.56 (s, 3/2 H, rotamer), 2.43-2.30 (m, 3 H), 2.20-2.10 (m, 1 H), 1.95-1.78 (m, 10 H), 1.66-1.64 (m, 2 H), 1.16-1.10 (m, 3 H). HRMS *m/z* $(M+H)^+$ calcd: 694.3039, obsd: 694.3051.

Example 500

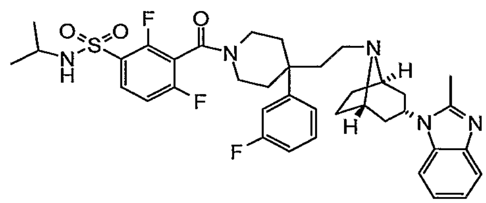
Preparation of 2,4-difluoro-3-[(4-(3-fluorophenyl)-4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)carbonyl]-N-propylbenzenesulfonamide



2,4-Difluoro-3-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)carbonyl]-*N*-propylbenzenesulfonamide (42mg, 59%) was obtained as solid from 2,6-difluoro-3-(chlorosulfonyl) benzoic acid (52 mg, 0.2 mmol), propylamine (18 μL,0.22mmol) and 1-((1*R*,5*S*)-8-{2-[4-(3-fluorophenyl) piperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1*H*-benzimidazole dihydrochloride (52 mg, 0.1 mmol) following the procedure outlined in example 473. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95-7.91 (m, 1 H), 7.65 (d, J=8.0 Hz, 1 H), 7.39-7.35 (m, 1 H), 7.30 –7.29 (m, 1 H), 7.16-7.14 (m, 2 H), 7.12-7.04 (m, 2 H), 6.96-6.95 (m, 2 H), 5.05-4.97 (two sets of multiplets, 1 H, rotamers), 4.63-4.57 (m, 1 H), 4.26-4.23 (m, 1 H), 3.41-3.35 (m, 2 H), 3.25-3.21 (m, 4 H), 3.04-2.90 (m, 2 H), 2.57 (s, 3/2 H, rotamer), 2.56 (s, 3/2 H, rotamer), 2.39-2.34 (m, 3 H), 2.20-2.10 (m, 1 H), 1.97-1.80 (m, 10 H), 1.65-1.63 (m, 2 H), 1.54-1.49 (m, 2 H), 0.90-0.85 (m, 3 H). HRMS *m/z* $(M+H)^+$ calcd: 708.3195, obsd: 708.3189.

Example 501

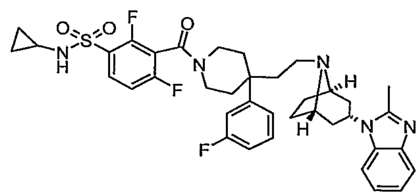
Preparation of 2,4-difluoro-3-[(4-(3-fluorophenyl)-4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)carbonyl]-N-isopropylbenzenesulfonamide



2,4-Difluoro-3-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)carbonyl]-*N*-isopropylbenzenesulfonamide (40 mg, 56%) was obtained as solid from 2,6-difluoro-3-(chloro sulfonyl)benzoic acid (52 mg, 0.2 mmol), isopropylamine (19 μL,0.22mmol) and 1-((1*R*,5*S*)-8-{2-[4-(3-fluorophenyl)piperidin-4-yl]ethyl}-8-azabicyclo [3.2.1]oct-3-yl)-2-methyl-1*H*-benzimidazole dihydrochloride (52 mg, 0.1 mmol) following the procedure outlined in example 473. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (q, J=7.3 Hz, 1 H), 7.65 (d, J=7.1 Hz, 1 H), 7.36 (q, J=7.7 Hz, 1 H), 7.29 (d, J=7.7 Hz, 1 H), 7.19-7.12 (m, 2 H), 7.10-7.04 (m, 2 H), 7.00-6.94 (m, 2 H), 4.91 (d, J=7.7 Hz, ½ H, rotamer), 4.86 (d, J=7.7 Hz, ½ H, rotamers), 4.62-4.59 (m, 1 H), 4.26-4.22 (m, 1 H), 3.55-3.50 (m, 1 H), 3.41-3.37 (m, 2 H), 3.24-3.19 (m, 3 H), 2.57 (s, 3/2 H, rotamer), 2.56 (s, 3/2 H, rotamer), 2.42-2.29 (m, 3 H), 2.17-2.14 (m, 1 H), 1.96-1.77 (m, 10 H), 1.66-1.65 (m, 2 H), 1.18 (dd, J=15, 6.6 Hz, 3 H, rotamer), 1.06 (dd, J=15, 6.6 Hz, 3 H, rotamer). HRMS *m/z* $(M+H)^+$ calcd: 708.3195, obsd: 708.3201.

Example 502

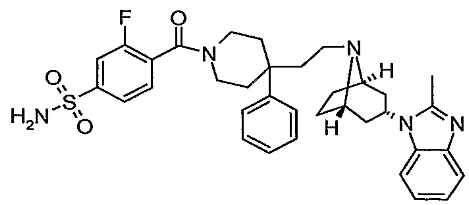
Preparation of N-cyclopropyl-2,4-difluoro-3-[(4-(3-fluorophenyl)-4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)carbonyl]benzenesulfonamide



N-Cyclopropyl-2,4-difluoro-3-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)carbonyl]benzenesulfonamide (40 mg, 53%) was obtained as solid from 2,6-difluoro-3-(chlorosulfonyl)benzoic acid (52 mg, 0.2 mmol), cyclopropyl amine (14 μL, 0.2mmol) and 1-((1*R*,5*S*)-8-{2-[4-(3-fluorophenyl)piperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1*H*-benzimidazole dihydrochloride (52 mg, 0.1 mmol) following the procedure outlined in example 473. ^{1}H NMR (400 MHz, $CDCl_3$), δ 7.98-7.96 (m, 1 H), 7.65 (d, J=8.8 Hz, 1 H), 7.38-7.33 (m, 1 H), 7.31-7.26 (m, 1 H), 7.19-7.12 (m, 2 H), 7.10-7.06 (m, 2 H), 7.04-6.94 (m, 2 H), 5.55 (s, ½ H, rotamer), 5.49 (s, ½ H, rotamer), 4.64-4.58 (m, 1 H), 4.27-4.22 (m, 1 H), 3.42-3.35 (m, 2 H), 3.25-3.19 (m, 3 H), 2.57 (s, 3/2 H, rotamer), 2.56 (s, 3/2 H, rotamer), 2.41-2.14 (m, 5 H), 2.03-1.77 (m, 10 H0, 1.64 (J=7.9 Hz, 2 H), 0.78-0.73 (m, 1 H), 0.66-0.54 (m, 3 H). HRMS *m/z* $(M+H)^+$ calcd: 706.3038, obsd: 706.3044.

Example 503

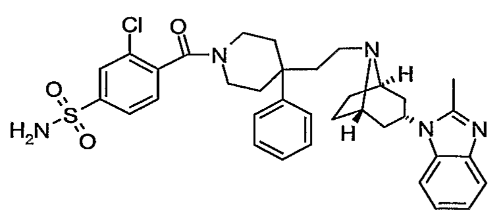
Preparation of 3-fluoro-4-[(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]benzene sulfonamide



3-Fluoro-4-[(4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]benzenesulfonamide (41 mg, 77%) was obtained as solid from 4-(aminosulfonyl)-2-fluorobenzoic acid (22 mg, 0.1 mmol), 2-methyl-1-{(1*R*,5*S*)-8-[2-(4-phenylpiperidin-4-yl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1*H*-benzimidazole dihydrochloride (51 mg, 0.1 mmol) and HATU (38mg, 0.1 mmol) following the procedure outlined in example 5. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (d, J=7.9 Hz, 1 H), 7.63-7.60 (m, 2 H), 7.40-7.36 (m, 2 H), 7.29-7.23 (m, 5 H), 7.18-7.12 (m, 2 H), 6.18 (br, 2 H), 4.61 (t, J=9 Hz, H), 4.21-4.18 (m, 1 H), 3.36- 3.18 (m, 5 H), 2.49 (s, 3 H), 2.39-2.19 (m, 4 H), 1.96-1.81 (m, 10 H), 1.62 (d, J=7.9 Hz, 2 H). HRMS *m/z* $(M+H)^+$ calcd: 630.2914, obsd: 630.2907.

Example 504

Preparation of 3-chloro-4-[(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]benzene sulfonamide

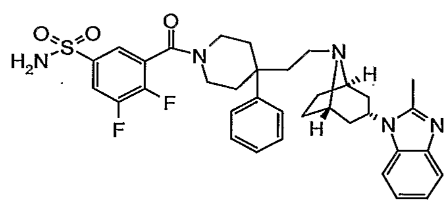


3-Chloro-4-[(4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-

yl)carbonyl]benzenesulfonamide (27mg, 42%) was obtained as solid from 4-(amino sulfonyl)-2-chlorobenzoic acid (24 mg, 0.1 mmol), 2-methyl-1-{(1*R*,5*S*)-8-[2-(4-phenylpiperidin-4-yl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1*H*-benzimidazole dihydrochloride (51 mg, 0.1 mmol) and HATU (38mg, 0.1 mmol) following the procedure outlined in example 5. ^{1}H NMR (400 MHz, $CDCl_3$), δ 7.95 (s, ½ H, rotamer), 7.91 (s, ½ H, rotamer), 7.81-7.76 (m, 1 H), 7.64-7.62 (m, 1 H), 7.41-7.36 (m, 2 H), 7.30-7.23 (m, 5 H), 7.19-7.09 (m, 2 H), 6.05 (br, 2 H), 4.62 (br, 1 H), 4.26-4.17 (m, 1 H), 3.48- 3.07 (m, 5 H), 2.50 (s, 3/2 H, rotamer), 2.49 (s, 3/2 H, rotamer), 2.37-2.08 (m, 4 H), 1.94-1.71 (m, 10 H), 1.62 (d, 2 H). HRMS *m/z* $(M+H)^+$ calcd: 646.2619, obsd: 646.2626.

Example 505

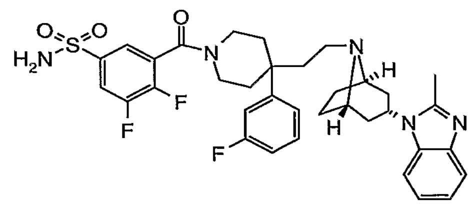
Preparation of 3,4-difluoro-5-[(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]benzene sulfonamide



3,4-Difluoro-5-[(4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]benzene sulfonamide (26mg, 40%) was obtained from 5-(aminosulfonyl)-2,3-difluorobenzoic acid (0.15mmol), 2-methyl-1-{(1*R*,5*S*)-8-[2-(4-phenylpiperidin-4-yl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1*H*-benzimidazole dihydrochloride (51 mg, 0.1 mmol) and HATU (38mg, 0.1 mmol) following the procedure outlined in example 473. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70-7.65 (m, 2 H), 7.47-7.37 (m, 3 H), 7.29-7.25 (m 4 H), 7.20-7.13 (m, 2 H), 4.84 (br, 1 H), 4.14-4.11 (m, 1 H), 3.65-3.20 (m, 6 H), 2.57 (s, 3 H), 2.53-2.48 (m, 2 H), 2.30-2.11 (m, 3 H), 1.97-1.71 (m, 11 H). HRMS *m/z* $(M+H)^+$ calcd: 648.2820, obsd: 648.2828.

Example 506

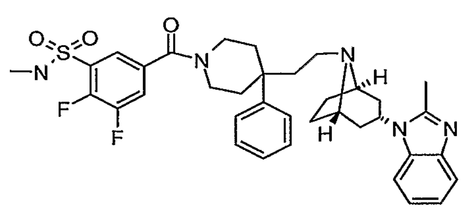
Preparation of 3,4-difluoro-5-[(4-(3-fluorophenyl)-4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)carbonyl]benzenesulfonamide



3,4-Difluoro-5-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)carbonyl]benzenesulfonamide (20mg, 30%) was obtained from 5-(aminosulfonyl)-2,3-difluorobenzoic acid (0.15mmol), 1-((1*R*,5*S*)-8-{2-[4-(3-fluorophenyl) piperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1*H*-benzimidazoledihydrochloride (52 mg, 0.1 mmol) and HATU (38mg, 0.1 mmol) following the procedure outlined in example 5. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69-7.62 (m, 2 H), 7.46-7.42 (m, 1 H), 7.39-7.33 (m, 1 H), 7.30-7.26 (m, 1 H), 7.21-7.13 (m, 2 H), 7.06 (d, J=7.9 Hz), 7.00-6.95 (m, 2 H), 5.86 (br, 2 H), 4.66-4.61 (m, 1 H), 4.14-4.09 (m, 1 H), 3.51 (br, 1 H), 3.29 (br, 4 H), 2.54 (s, 3 H), 2.49-2.13 (m, 5 H), 1.95-1.83 (m, 9 H), 1.67-1.65 (m, 2 H). HRMS *m/z* $(M+H)^+$ calcd: 666.2726, obsd: 666.2719.

Example 507

Preparation of 2,3-Difluoro-N-methyl-5-[(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1] oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]benzene sulfonamide

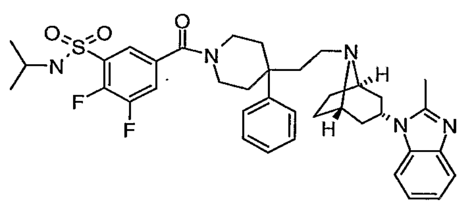


2,3-Difluoro-*N*-methyl-5-[(4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]benzene

sulfonamide (31 mg, 47%) was obtained as solid from 3-(chlorosulfonyl)-4,5-difluorobenzoic acid (52 mg, 0.2 mmol), methylamine (110 μL, 2.0 M in THF), 2-methyl-1-{(1*R*,5*S*)-8-[2-(4-phenylpiperidin-4-yl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1*H*-benzimidazole dihydro chloride (51 mg, 0.1 mmol) and HATU (38mg, 0.1 mmol) following the procedure outlined in example 473. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68-7.64 (m, 2 H), 7.50-7.45 (m, 1 H), 7.41-7.37 (m, 2 H), 7.30-7.24 (m 4 H), 7.19-7.12 (m, 2 H), 5.26 (br, 1 H), 4.66-4.6- (m, 1 H), 4.17 (br, 1 H), 3.51 (br, 1 H), 3.27 (br, 4 H), 2.75 (d, J=2.3 Hz, 3 H), 2.57 (s, 3 H), 2.42-2.34 (m, 3 H), 2.20 (br, 1 H), 2.01-1.75 (m, 10 H), 1.63 (d, J=7.90 Hz, 2 H). HRMS *m/z* $(M+H)^+$ calcd: 662.2976, obsd: 672.2985.

Example 508

Preparation of 2,3-difluoro-N-isopropyl-5-[(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]benzenesulfonamide

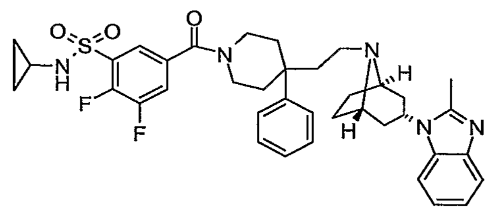


2,3-Difluoro-*N*-isopropyl-5-[(4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]benzene-sulfonamide (25 mg, 36%) was obtained as solid from 3-(chlorosulfonyl)-4,5-difluorobenzoic acid (52 mg, 0.2 mmol), isopropylamine (19 μL, 0.2 mmol), 2-methyl-1-{(1*R*,5*S*)-8-[2-(4-phenylpiperidin-4-yl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1*H*-benzimidazole dihydrochloride (51 mg, 0.1 mmol) and HATU (38mg, 0.1 mmol) following the procedure outlined in example 473. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69-7.65 (m, 2 H), 7.50-7.45 (m, 1 H), 7.41-7.37 (m, 2 H), 7.30-7.24 (m 4 H), 7.19-7.12 (m, 2 H), 4.90 (d, J=7.7 Hz, 1 H), 4.65 (m, 1 H), 4.18 (br, 1 H), 3.61-3.51 (m, 2 H), 3.26 (br, 4 H), 2.57 (s, 3 H), 2.43-2.35 (m, 3 H), 2.201-2.19 (m, 1 H), 1.94-1.85 (m, 10 H), 1.63 (d,

J=7.90 Hz, 2 H), 1.14 (d, J=6.6 Hz, 6 H). HRMS *m/z* $(M+H)^+$ calcd: 690.3289, obsd: 690.3309.

Example 509

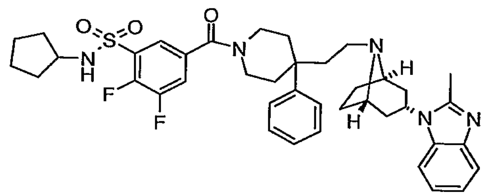
Preparation of N-cyclopropyl-2,3-difluoro-5-[(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]benzenesulfonamide



N-Cyclopropyl-2, 3-difluoro-5-[(4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]benzenesulfonamide (29 mg, 42%) was obtained as solid from 3-(chlorosulfonyl)-4,5-difluorobenzoic acid (52 mg, 0.2 mmol), isopropylamine (15 μL, 0.2 mmol), 2-methyl-1-{(1*R*,5*S*)-8-[2-(4-phenylpiperidin-4-yl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1*H*-benzimidazole dihydrochloride (51 mg, 0.1 mmol) and HATU (38mg, 0.1 mmol) following the procedure outlined in example 473. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72-7.71 (m, 1H), 7.66-7.64 (m, 1 H), 7.53-7.48 (m, 1 H), 7.41-7.37 (m, 2 H), 7.30-7.24 (m 4 H), 7.19-7.12 (m, 2 H), 5.61 (s, 1 H), 4.67-4.57 (m, 1 H), 4.18 (br, 1 H), 3.51 (br, 1 H), 3.27 (br, 4 H), 2.57 (s, 3 H), 2.42 -2.28 (m, 4H), 2.221-2.20 (m, 1 H), 1.94-1.76 (m, 10 H), 1.65-1.60 (m, 2 H), 0.71-0.61 (m, 4 H). HRMS *m/z* $(M+H)^+$ calcd: 688.3133, obsd: 688.3123.

Example 510

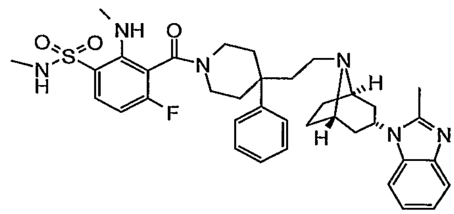
Preparation of N-cyclopentyl-2,3-difluoro-5-[(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]benzenesulfonamide



N-Cyclopentyl-2,3-difluoro-5-[(4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1] oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl] benzenesulfonamide (29 mg, 40%) was obtained as solid from 3-(chlorosulfonyl)-4,5-difluorobenzoic acid (52 mg, 0.2 mmol), isopentylamine (22 μL, 0.2 mmol), 2-methyl-1-{(1*R*,5*S*)-8-[2-(4-phenylpiperidin-4-yl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1*H*-benzimidazole dihydrochloride (51 mg, 0.1 mmol) and HATU (38mg, 0.1 mmol) following the procedure outlined in example 473. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69-7.65 (m, 2 H), 7.50-7.46 (m, 1 H), 7.41-7.37 (m, 2 H), 7.30-7.24 (m 4 H), 7.19-7.12 (m, 2 H), 5.01 (d, J=7.3 Hz, 1 H), 4.68-4.64 (m, 1 H), 4.18 (br, 1 H), 3.69-3.64 (m, 1 H), 3.51 (br, 1 H), 3.29 (br, 4 H), 2.57 (s, 3 H), 2.44-2.36 (m, 3 H), 2.20-2.18 (m, 1 H), 1.97-1.70 (m, 12 H), 1.69-1.60 (m, 4 H), 1.57-1.47 (m, 2 H), 1.45-1.24 (m, 2 H). HRMS *m/z* $(M+H)^+$ calcd: 716.3446, obsd: 716.3456.

Example 511

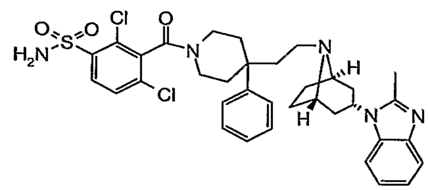
Preparation of 4-fluoro-N-methyl-2-(methylamino)-3-[(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]benzenesulfonamide



4-Fluoro-*N*-methyl-2-(methylamino)-3-[(4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]benzenesulfonamide (20mg, 30%) was obtained as solid from 6-fluoro-2-(methylamino)-3-[(methyl amino)sulfonyl]benzoic acid (205 mg, 0.8 mmol), 2-methyl-1-{(1*R*,5*S*)-8-[2-(4-phenylpiperidin-4-yl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1*H*-benzimidazole dihydro- chloride (51 mg, 0.1 mmol) and HATU (38mg, 0.1 mmol) following the procedure outlined in example 473. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79-7.74 (m, 1 H), 7.66-7.64 (m, 1 H), 7.41-7.34 (m, 2 H), 7.30-7.21 (m 4 H), 7.19-7.04 (m, 3 H), 6.95-6.40 (m, 1 H), 6.29-6.18 (m, 1 H), 5.07-4.93 (m, 1 H), 4.64 (br, 1 H), 4.37-4.08 (m, 1 H), 3.57-3.34 (m, 1 H), 3.39-3.12 (m, 4 H), 3.00 (d, J=5.4 Hz, 3/2 H, rotamer), 2.75 (d, J=5.2 Hz, 3/2 H, rotamer), 2.58-2.56 (m, 3 H), 2.41-2.07 (m, 4 H), 1.93-1.68 (m, 12 H), 1.63-1.61(m, 2 H). HRMS *m/z* $(M+H)^+$ calcd: 673.3336, obsd: 673.3345.

Example 512

Preparation of 2,4-dichloro-3-[(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]benzene-sulfonamide

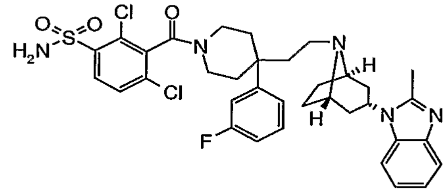


2,4-Dichloro-3-[(4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]benzene sulfonamide (36mg, 53%) was obtained as solid from 3-(aminosulfonyl)-2,6-dichlorobenzoic acid (51 mg, 0.15 mmol), 2-methyl-1-{(1*R*,5*S*)-8-[2-(4-phenylpiperidin-4-yl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1*H*-benzimidazole dihydrochloride (51 mg, 0.1 mmol) and HATU (38mg, 0.1 mmol) following the procedure outlined in example 473.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99-7.94 (d, J=8.4 Hz, 1 H), 7.63-7.61 (d, J=7.2 Hz, 1 H), 7.43-7.36 (m, 3 H), 7.29-7.26 (m, 4 H), 7.18-7.08 (m, 2 H), 5.96 (br, 2 H), 4.63 (br, 1 H), 4.29-4.24 (m, 1 H), 3.40-3.12 (m, 5 H), 2.53 (s, 3 H), 2.48-2.36 (m, 3 H), 2.24-2.21 (m, 1 H), 1.99-1.84 (m, 9 H), 1.64-1.61(m, 2 H). HRMS *m/z* $(M+H)^+$ calcd: 680.2229, obsd: 680.2228.

Example 513

Preparation of 2,4-dichloro-3-[(4-(3-fluorophenyl)-4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)carbonyl]benzenesulfonamide

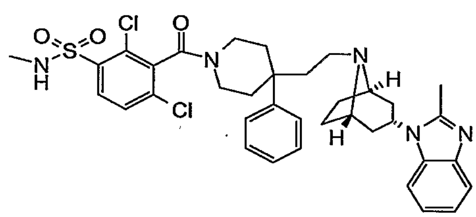


2,4-Dichloro-3-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo [3.2.1]oct-8-yl]ethyl}piperidin-1-yl)carbonyl]benzene sulfonamide (30mg, 43%) was obtained as solid from 3-

(aminosulfonyl)-2,6-dichlorobenzoic acid (51 mg, 0.15 mmol), 2-methyl-1-{(1*R*,5*S*)-8-[2-(4-(3-fluorophenyl) piperidin-4-yl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1*H*-benzimidazole dihydrochloride (52 mg, 0.1 mmol) and HATU (38mg, 0.1 mmol) following the procedure outlined in example 473. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01-7.99 (m, 1 H), 7.64-7.62 (m, 1 H), 7.45-7.35 (m, 2 H), 7.34-7.28 (m, 1 H), 7.22-7.12 (m, 2 H), 7.08-7.06 (m, 1 H), 6.99-6.95 (m, 2 H), 5.79 (br, 2 H), 4.65-4.55 (m, 1 H), 4.27-4.23 (m, 1 H), 3.43-3.12 (m, 5 H), 2.54 (s, 3 H), 2.41-2.37 (m, 4 H), 2.19-2.16 (m, 1 H), 1.94-1.83 (m, 9 H), 1.66-1.65 (m, 2 H). HRMS *m/z* $(M+H)^+$ calcd: 698.2135, obsd: 698.2141.

Example 514

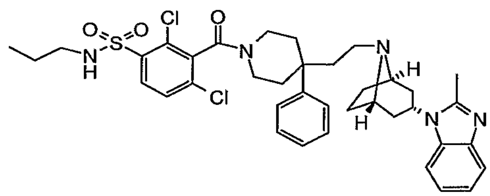
Preparation of 2,4-dichloro-N-methyl-3-[(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1] oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]benzene sulfonamide



2,4-Dichloro-*N*-methyl-3-[(4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]benzene sulfonamide (33mg, 48%) was obtained as solid from 2,6-dichloro-3-(chlorosulfonyl)benzoic acid (58 mg, 0.20 mmol), methylamine (120 μL, 2.0 M in THF), 2-methyl-1-{(1*R*,5*S*)-8-[2-(4-phenylpiperidin-4-yl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1*H*-benzimidazole dihydrochloride (51 mg, 0.1 mmol) and HATU (38mg, 0.1 mmol) following the procedure outlined in example 473. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06-8.03 (m, 1 H), 7.66-7.64 (m, 1 H), 7.52-7.44 (m, 1 H), 7.41-7.37 (m, 2 H), 7.30-7.24 (m, 4 H), 7.19-7.12 (m, 2 H), 5.31-5.13 (m, 1 H), 4.64 (br, 1 H), 4.34-4.25 (m, 1 H), 3.43-3.12 (m, 5 H), 2.68-2.63 (m, 3 H), 2.57-2.55 (m, 3 H), 2.39-2.34 (m, 3 H), 2.26-2.20 (m, 1 H), 1.99-1.82 (m, 10 H), 1.63-1.62(m, 2 H). HRMS *m/z* $(M+H)^+$ calcd: 694.2385, obsd: 694.2391.

Example 515

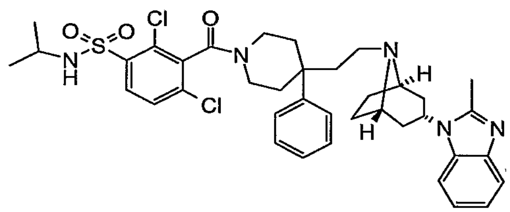
Preparationo of 2,4-dichloro-3-[(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]-N-propylbenzenesulfonamide



2,4-Dichloro-3-[(4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]-*N*-propylbenzenesulfonamide (19mg, 26%) was obtained as solid from 2,6-dichloro-3-(chlorosulfonyl)benzoic acid (58 mg, 0.20 mmol), propylamine (20 μL, 0.24 mmol), 2-methyl-1-{(1*R*,5*S*)-8-[2-(4-phenylpiperidin-4-yl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1*H*-benzimidazole dihydrochloride (51 mg, 0.1 mmol) and HATU (38mg, 0.1 mmol) following the procedure outlined in example 473. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06-8.04 (m, 1 H), 7.65 (d, 1 H), 7.52-7.41 (m, 1 H), 7.39-7.32 (m, 2 H), 7.29-7.21 (m, 4 H), 7.19-7.12 (m, 2 H), 5.29-4.98 (m, 1 H), 4.63 (br, 1 H), 4.33-4.27 (m, 1 H), 3.42-3.12 (m, 5 H), 3.04-2.88 (m, 2 H), 2.86-2.77 (m, 1 H), 2.58-2.56 (m, 3 H), 2.40-2.37 (m, 3 H), 2.26-2.19 (m, 1 H), 1.93-1.63 (m, 14 H), 1.57-1.51(m, 2 H), 0.92-0.85 (m, 3 H). HRMS *m/z* $(M+H)^+$ calcd: 722.2698, obsd: 722.2686.

Example 516

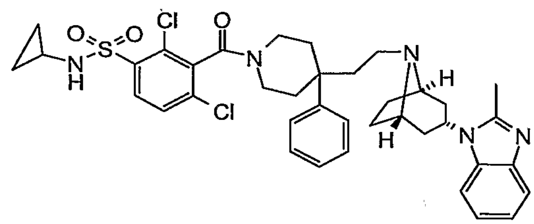
Preparation of 2,4-dichloro-N-isopropyl-3-[(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]benzenesulfonamide



2,4-Dichloro-*N*-isopropyl-3-[(4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]benzene sulfonamide (20 mg, 28%) was obtained as solid from 2,6-dichloro-3-(chlorosulfonyl)benzoic acid (58 mg, 0.20 mmol), isopropylamine (20.5 μL, 0.24 mmol), 2-methyl-1-{(1*R*,5*S*)-8-[2-(4-phenylpiperidin-4-yl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1*H*-benzimidazole dihydrochloride (51 mg, 0.1 mmol) and HATU (38mg, 0.1 mmol) following the procedure outlined in example 473. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08-8.05 (m, 1 H), 7.66-7.65 (m, 1 H), 7.51-7.44 (m, 1 H), 7.41-7.37 (m, 2 H), 7.30-7.25 (m, 4 H), 7.20-7.12 (m, 2 H), 4.95-4.83 (m, 1 H), 4.64-4.62 (m, 1 H), 4.32-4.27 (m, 1 H), 3.49-3.34 (m, 2 H), 3.27-3.24 (m, 3 H), 3.19-3.14 (m, 1 H), 2.57-2.56 (m, 3 H), 2.40-2.37 (m, 3 H), 2.26-2.18 (m, 1 H), 1.96-1.82 (m, 10 H), 1.64-1.62 (m, 2 H), 1.21-1.02 (m, 6 H). HRMS *m/z* $(M+H)^+$ calcd: 722.2698, obsd: 722.2702.

Example 517

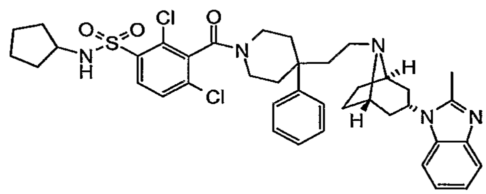
Preparation of 2,4-dichloro-N-cyclopropyl-3-[(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]benzenesulfonamide



2,4-Dichloro-*N*-cyclopropyl-3-[(4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1] oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]benzene sulfonamide (35 mg, 49%) was obtained as solid from 2,6-dichloro-3-(chlorosulfonyl)benzoic acid (58 mg, 0.20 mmol), cyclopropylamine (17 μL, 0.24 mmol), 2-methyl-1-{(1*R*,5*S*)-8-[2-(4-phenylpiperidin-4-yl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1*H*-benzimidazole dihydrochloride (51 mg, 0.1 mmol) and HATU (38mg, 0.1 mmol) following the procedure outlined in example 473. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12-8.09 (m, 1 H), 7.66-7.65 (m, 1 H), 7.54-7.46 (m, 1 H), 7.41-7.37 (m, 2 H), 7.30-7.25 (m, 4 H), 7.19-7.12 (m, 2 H), 5.67-5.54 (m, 1 H), 4.64 (br, 1 H), 4.33-4.27 (m, 1 H), 3.43-3.12 (m, 5 H), 2.58-2.56 (m, 3 H), 2.40-2.37 (m, 3 H), 2.26-2.19 (m, 2 H), 2.04-1.82 (m, 10 H), 1.64-1.63 (m, 2 H), 0.85-0.76 (m, 1 H), 0.67-0.54 (m, 3 H). HRMS *m/z* $(M+H)^+$ calcd: 720.2542, obsd: 720.2558.

Example 518

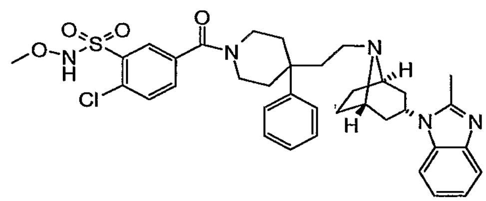
Preparation of 2,4-dichloro-N-cyclopentyl-3-[(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]benzenesulfonamide



2,4-Dichloro-*N*-cyclopentyl-3-[(4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1] oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl] benzenesulfonamide (28mg, 37%) was obtained as solid from 2,6-dichloro-3-(chlorosulfonyl)benzoic acid (58 mg, 0.20 mmol), cyclopentylamine (20 μL, 0.24 mmol), 2-methyl-1-{(1*R*,5*S*)-8-[2-(4-phenylpiperidin-4-yl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1*H*-benzimidazole dihydrochloride (51 mg, 0.1 mmol) and HATU (38mg, 0.1 mmol) following the procedure outlined in example 473. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08-8.06 (m, 1 H), 7.67-7.65 (m, 1 H), 7.52-7.44 (m, 1 H), 7.41-7.34 (m, 2 H), 7.29-7.25 (m, 4 H), 7.19-7.12 (m, 2 H), 5.09-4.96 (m, 1 H), 4.62 (br, 1 H), 4.31-4.28 (m, 1 H), 3.60-3.50 (m. 1 H), 3.42-3.11 (m, 5 H), 2.58-2.53 (m, 3 H), 2.40-2.37 (m, 4 H), 2.25-2.18 (m, 1 H), 1.99-1.75 (m, 11 H), 1.73-1.49 (m, 8 H). HRMS *m/z* $(M+H)^+$ calcd: 748.2855, obsd: 748.2863.

Example 519

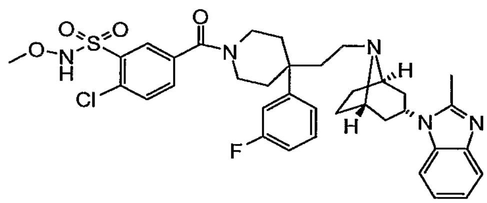
Preparation of 2-chloro-N-methoxy-5-[(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]benzene sulfonamide



2-Chloro-*N*-methoxy-5-[(4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]benzene sulfonamide (17 mg, 25%) was obtained as solid from 4-chloro-3-(chlorosulfonyl)benzoic acid (50 mg, 0.2 mmol), methoxyamine hydrochloride (21 mg, 0.20 mmol), 2-methyl-1-{(1*R*,5*S*)-8-[2-(4-phenylpiperidin-4-yl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1*H*-benzimidazole dihydrochloride (51 mg, 0.1 mmol) and HATU (38mg, 0.1 mmol) following the procedure outlined in example 473. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (d, J= 2.0 Hz, 1 H), 8.09 (br, 1, H), 7.67-7.57 (m, 3 H), 7.41-7.37 (m, 2 H), 7.30-7.24 (m, 4 H), 7.19-7.09 (m, 2 H), 4.67 (br, 1 H), 4.21-4.19 (m, 1 H), 3.77 (s, 3 H), 3.53-3.50 (m, 1 H), 3.35-3.28 (m, 4 H), 2.57 (s, 3 H), 2.39 (br, 3 H), 2.20-2.17 (m, 1 H), 1.95-1.77 (m, 10 H), 1.66-1.64 (m, 2 H). HRMS *m/z* $(M+H)^+$ calcd: 676.2724, obsd: 676.2727.

Example 520

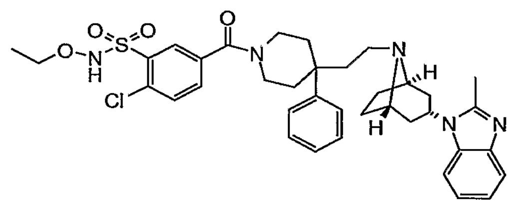
Preparation of 2-chloro-5-[(4-(3-fluorophenyl)-4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)carbonyl]-N-methoxybenzenesulfonamide



2-Chloro-5-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)carbonyl]-*N*-methoxybenzenesulfonamide (10 mg, 14%) was obtained as solid from 4-chloro-3-(chloro sulfonyl)benzoic acid (50 mg, 0.2 mmol), methoxyamine hydrochloride (21mg, 0.20 mmol), 1-((1*R*,5*S*)-8-{2-[4-(3-fluorophenyl)piperidin-4-yl]ethyl}-8-azabicyclo [3.2.1]oct-3-yl)-2-methyl-1*H*-benzimidazole dihydrochloride (52 mg, 0.1 mmol) and HATU (38mg, 0.1 mmol) following the procedure outlined in example 473. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (d, J= 1.6 Hz, 1 H), 7.92 (br, 1, H), 7.71-7.59 (m, 3 H), 7.38 (q, J=7.7 Hz, 1 H), 7.30-7.26 (m, 1 H), 7.20--7.13 (m, 2 H), 7.08 (d, J=8.1 Hz, 1 H), 7.01-6.96 (m, 2 H), 4.67 (br, 1 H), 4.14-4.11 (m, 1 H), 3.78 (s, 3 H), 3.59 (br, 1 H), 3.54-3.31 (br, 4 H), 2.59 (s, 3 H), 2.44 (br, 2 H), 2.28 (br, 2 H), 2.11 (br, 2 H), 1.97-1.65 (m, 10 H). HRMS *m/z* $(M+H)^+$ calcd: 694.2630, obsd: 694.2630.

Example 521

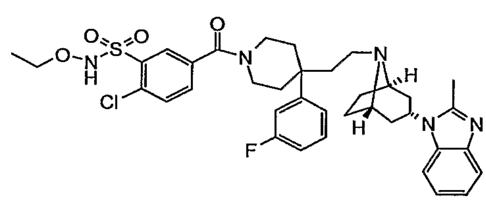
Preparation of 2-chloro-N-ethoxy-5-[(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]benzene sulfonamide



2-Chloro-*N*-ethoxy-5-[(4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]benzene-sulfonamide (6 mg, 8%) was obtained as solid from 4-chloro-3-(chlorosulfonyl)benzoic acid (50 mg, 0.2 mmol), ethoxyamine hydrochloride (29 mg, 0.20 mmol), 2-methyl-1-{(1*R*,5*S*)-8-[2-(4-phenylpiperidin-4-yl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1*H*-benzimidazole dihydrochloride (51 mg, 0.1 mmol) and HATU (38mg, 0.1 mmol) following the procedure outlined in example 473. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (s, 1 H), 7.80 (s, 1 H), 7.67-7.59 (m, 3 H), 7.41-7.38 (m, 2 H), 7.30-7.26 (m, 3 H), 7.20-7.12 (m, 2 H), 4.69 (br, 1 H), 4.21 (br, 1 H), 4.03 (q, J=7.0 Hz, 2 H), 3.51 (br, 1 H), 3.29 (br, 4 H), 2.58 (s, 3 H), 2.42-2.39 (m, 3 H), 2.16 (br, 1 H), 1.94 (br, 7 H), 1.69 (br, 5 H), 1.16 (t, J=7.0 Hz, 3 H). HRMS *m/z* $(M+H)^+$ calcd: 690.2881, obsd: 690.2878.

Example 522

Preparation of 2-chloro-N-ethoxy-5-[(4-(3-fluoro phenyl)-4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)carbonyl]benzenesulfonamide

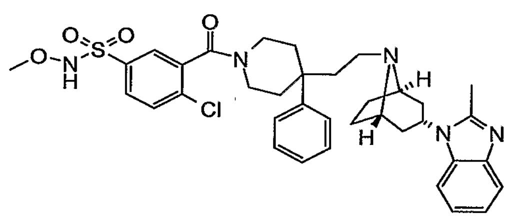


2-Chloro-*N*-ethoxy-5-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)

carbonyl]benzenesulfonamide (12mg, 17%) was obtained as solid from 4-chloro-3-(chlorosulfonyl)benzoic acid (50 mg, 0.2 mmol), ethoxyamine hydrochloride (29 mg, 0.20 mmol), 1-((1*R*,5*S*)-8-{2-[4-(3-fluorophenyl)piperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1*H*-benzimidazole dihydrochloride (52 mg, 0.1 mmol) and HATU (38mg, 0.1 mmol) following the procedure outlined in example 473. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 (d, J= 1.8 Hz, 1 H), 7.82 (br, 1, H), 7.67-7.59 (m, 3 H), 7.37 (q, J=7.8 Hz, 1 H), 7.29 (d, J=7.7 Hz, 1 H), 7.20--7.13 (m, 2 H), 7.08 (d, J=8.1 Hz, 1 H), 7.01-6.96 (m, 2 H), 4.81 (br, 1 H), 4.17 (br, 1 H), 4.04 (q, J=7.1 Hz, 2 H), 3.53 (br, 1 H), 3.39-3.31 (br, 4 H), 2.59 (s, 3 H), 2.43 (br, 2 H), 2.29 (br, 1 H), 2.10 (br, 2 H), 1.97-1.93 (m, 8 H), 1.71 (br, 4 H), 1.16 (t, J=7.0 Hz, 3 H). HRMS *m/z* $(M+H)^+$ calcd: 708.2787, obsd: 708.2797.

Example 523

Preparation of 4-chloro-N-methoxy-3-[(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]benzene-sulfonamide

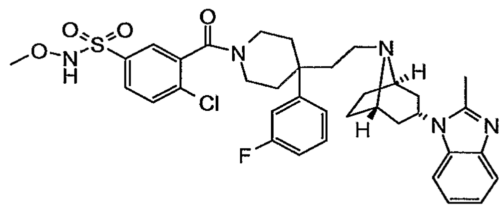


4-Chloro-*N*-methoxy-3-[(4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]benzene sulfonamide (2mg) was obtained as solid from 2-chloro-5-(chlorosulfonyl)benzoic acid (50 mg, 0.2 mmol), methoxyamine hydrochloride (21 mg, 0.20 mmol), 2-methyl-1-{(1*R*,5*S*)-8-[2-(4-phenylpiperidin-4-yl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1*H*-benzimidazole dihydrochloride (51 mg, 0.1 mmol) and HATU (38mg, 0.1 mmol) following the procedure outlined in example 473. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90-7.85 (m, 2 H), 7.66 (d, J=7.5 Hz, 1 H), 7.57 (m, 1 H), 7.42-7.33 (m, 2 H), 7.30-7.26 (m, 4 H), 7.20-7.12 (m, 3 H), 4.70 (br, 1 H), 4.30-4.22 (m, 1 H), 3.80 (d, J=7.1 Hz, 3 H), 3.42-3.09 (m,

7 H), 2.56 (s, 3 H), 2.43 –2.08 (m, 4 H), 1.95-1.90 (m, 8 H), 1.89-1.75 (m, 3 H). HRMS *m/z* $(M+H)^+$ calcd: 676.2724, obsd: 676.2722.

Example 524

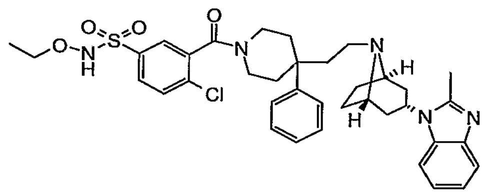
Preparation of 4-chloro-3-[(4-(3-fluorophenyl)-4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)carbonyl]-N-methoxybenzenesulfonamide



4-Chloro-3-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*) -3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1] oct-8-yl]ethyl}piperidin-1-yl)carbonyl]-*N*-methoxy benzenesulfonamide (3.9 mg) was obtained as solid from 2-chloro-5-(chlorosulfonyl)benzoic acid (50 mg, 0.2 mmol), ethoxyamine hydrochloride (29 mg, 0.20 mmol), 1-((1*R*,5*S*)-8-{2-[4-(3-fluorophenyl)piperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1*H*-benzimidazole dihydrochloride (52 mg, 0.1 mmol) and HATU (38mg, 0.1 mmol) following the procedure outlined in example 473. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89-7.85 (m, 2 H), 7.66 (d, J=7.7 Hz, 1 H), 7.61-7.55 (m, 1 H), 7.38-7.36 (m, 1 H), 7.31-7.29 (m, 1 H), 7.21-7.14 (m, 3 H), 7.10-7.05 (m, 1 H), 6.99-6.97 (m, 2 H), 4.68 –4.63 (m, 1 H), 4.27-4.23 (m, 1 H), 3.80 (d, J=4 Hz, 3 H), 3.43-3.20 (m, 5 H), 3.18-3.09 (m, 1 H), 2.56 (s, 3 H), 2.43-2.30 (m, 4 H), 2.16-2.13 (m, 1 H), 1.96-1.89 (m, 10 H). HRMS *m/z* $(M+H)^+$ calcd: 694.2630, obsd: 694.2625.

Example 525

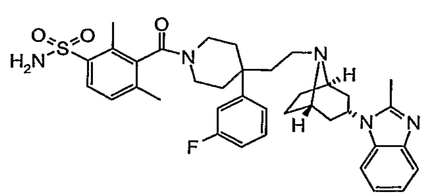
Preparation of 4-chloro-N-ethoxy-3-[(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]benzene-sulfonamide



4-Chloro-*N*-ethoxy-3-[(4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]benzene-sulfonamide (3.1 mg) was obtained as solid from 2-chloro-5-(chlorosulfonyl)benzoic acid (50 mg, 0.2 mmol), ethoxyamine hydrochloride (29 mg, 0.20 mmol), 2-methyl-1-{(1*R*,5*S*)-8-[2-(4-phenylpiperidin-4-yl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1*H*-benzimidazole dihydrochloride (51 mg, 0.1 mmol) and HATU (38mg, 0.1 mmol) following the procedure outlined in example 473. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90-7.84 (m, 1 H), 7.65 (d, J=7.5 Hz, 1 H), 7.60-7.53 (m, 1 H), 7.41-7.32 (m, 2 H), 7.30-7.26 (m, 5 H), 7.19-7.14 (m, 3 H), 4.65 (br, 1 H), 4.30-4.22 (m, 1 H), 4.06-4.02 (m, 2 H), 3.33-3.25 (m, 5 H), 2.55 (s, 3 H), 2.38 (br, 3 H), 2.11-2.08 (m, 1 H), 1.99-1.89 (m, 9 H), 1.87-1.64 (m, 2 H), 1.22- 1.15 (m, 3 H). HRMS *m/z* $(M+H)^+$ calcd: 690.2881, obsd: 690.2880.

Example 526

Preparation of 3-[(4-(3-fluorophenyl)-4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)carbonyl]-2,4-dimethylbenzene sulfonamide

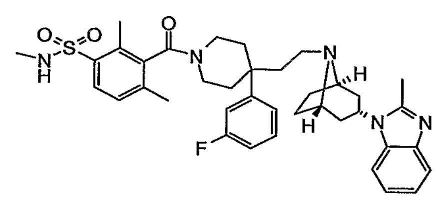


3-[(4-(3-Fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)carbonyl]-2,4-

dimethylbenzene sulfonamide (25 mg, 38%) was obtained as solid from 3-(aminosulfonyl)-2,6-dimethylbenzoic acid (23 mg, 0.1 mmol), 1-((1*R*,5*S*)-8-{2-[4-(3-fluorophenyl)piperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1*H*-benzimidazole dihydrochloride (52 mg, 0.1 mmol) and HATU (38mg, 0.1 mmol) following the procedure outlined in example 5. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (d, J=8.2 Hz, 1 H), 7.64 (d, J=7.2 Hz, 1 H), 7.36 (q, J=7.9 HZ, 1 H), 7.29 (d, J=7.4 Hz, 1 H), 7.19-7.10 (m, 3 H), 7.05 (d, J=7.9 HZ, 1 H), 6.99-6.95 (m, 2 H), 5.20 (br, 2 H), 4.61-4.56 (m, 1 H), 4.27-4.23 (m, 1 H), 3.46-3.41 (m, 1 H), 3.23 (br, 3 H), 3.10-3.05 (m, 1 H), 2.60 (s, 3/2 H, rotamer), 2.53 (s, 3 H), 2.41 (s, 3/2 H, rotamer), 2.37 (s, 3/2 H, rotamer), 2.33-2.29 (m, 2 H), 2.19 (s, 3/2 H, rotamer), 2.11-2.08 (m, 1 H), 1.94-1.82 (m, 10 H), 1.74-1.62 (m, 3 H). HRMS *m/z* $(M+H)^+$ calcd: 658.3227, obsd: 658.3223.

Example 527

Preparation of 3-[(4-(3-fluorophenyl)-4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)carbonyl]-N,2,4-trimethyl benzenesulfonamide

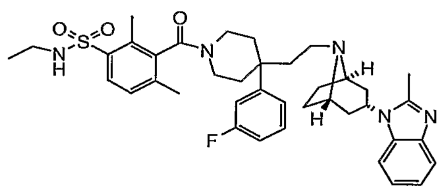


3-[(4-(3-Fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)carbonyl]-*N*-2,4-trimethyl benzenesulfonamide (10 mg, 15%) was obtained as solid from 3-(chlorosulfonyl)-2,6-dimethylbenzoic acid (50 mg, 0.2 mmol), methylamine (120 μL, 2.0 M in THF), 1-((1*R*,5*S*)-8-{2-[4-(3-fluorophenyl)piperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1*H*-benzimidazole dihydrochloride (52 mg, 0.1 mmol) and HATU (38mg, 0.1 mmol) following the procedure outlined in example 473. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91-7.88 (m, 1 H), 7.66 (d, J=7.7 Hz, 1 H), 7.36 (q, J=7.7 HZ, 1 H), 7.29 (d, J=7.5 Hz, 1 H), 7.22-7.14 (m, 3 H), 7.05 (d, J=7.9 HZ, 1 H), 6.99-6.95 (m, 2 H), 4.63-4.52

(m, 2 H), 4.33-4.29 (m, 1 H), 3.43-3.34 (m, 1 H), 3.25 (br, 3 H), 3.05 (q, J=10.6 Hz, 1 H), 2.64-2.55 (m, 8 H), 2.42-4.21 (m, 7 H), 2.08 (br, 1 H), 1.95-1.88 (m, 6 H), 1.84-1.63 (m, 6 H). HRMS *m/z* $(M+H)^+$ calcd: 672.3384, obsd: 672.3400.

Example 528

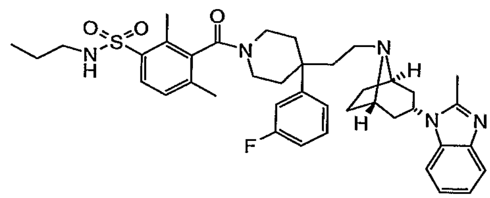
Preparation of N-ethyl-3-[(4-(3-fluorophenyl)-4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)carbonyl]-2,4-dimethylbenzenesulfonamide



N-Ethyl-3-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1] oct-8-yl]ethyl}piperidin-1-yl)carbonyl]-2,4-dimethyl benzenesulfonamide (9.2mg, 14%) was obtained as solid from 3-(chlorosulfonyl)-2,6-dimethylbenzoic acid (50 mg, 0.2 mmol), ethylamine (120 μL, 2.0 M in THF), 1-((1*R*,5*S*)-8-{2-[4-(3-fluorophenyl)piperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1*H*-benzimidazole dihydrochloride (52 mg, 0.1 mmol) and HATU (38mg, 0.1 mmol) following the procedure outlined in example 473. ^1H NMR (400 MHz, $CDCl_3$) δ 7.89 (d, J=8.0 Hz, 1 H), 7.66 (d, J=7.3 Hz, 1 H), 7.36 (q, J=7.7 Hz, 1 H), 7.30 (d, J=8.1 Hz, 1 H), 7.21-7.13 (m, 3 H), 7.06 (d, J=7.9 HZ, 1 H), 6.99-6.95 (m, 2 H), 4.63-4.59 (m, 1 H), 4.51-4.49 (m, 1 H), 4.33-4.29 (m, 1 H), 3.40-3.34 (m, 1 H), 3.25-3.21 (m, 3 H), 3.11-3.05 (m, 1 H), 2.94-2.87 (m, 1 H), 2.62 (s, 3 H), 2.57 (s, 3 H), 2.55-2.30 (m, 3 H), 2.20 (s, 3 H), 2.09-2.06 (m, 1 H), 1.95-1.88 (m, 6 H), 1.84-1.63 (m, 6 H), 1.12 (t, J=7.2 Hz, 3 H). HRMS *m/z* $(M+H)^+$ calcd: 686.3540, obsd: 686.3522.

Example 529

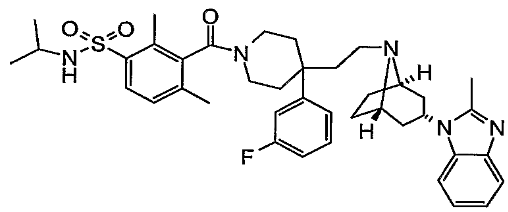
Preparation of 3-[(4-(3-fluorophenyl)-4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)carbonyl]-2,4-dimethyl-N-propylbenzenesulfonamide



3-[(4-(3-Fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)carbonyl]-2,4-dimethyl-*N*-propylbenzenesulfonamide (8 mg, 12%) was obtained as solid from 3-(chlorosulfonyl)-2,6-dimethylbenzoic acid (50 mg, 0.2 mmol), propylamine (18μL, 0.22 mmol), 1-((1*R*,5*S*)-8-{2-[4-(3-fluorophenyl)piperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1*H*-benzimidazole dihydrochloride (52 mg, 0.1 mmol) and HATU (38mg, 0.1 mmol) following the procedure outlined in example 473. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91-7.88 (m, 1 H), 7.66 (d, J=7.7 Hz, 1 H), 7.36 (q, J=7.6 HZ, 1 H), 7.33-7.31 (m, 1 H), 7.21-7.13 (m, 3 H), 7.06 (d, J=7.3 HZ, 1 H), 6.99-6.95 (m, 2 H), 4.63-4.59 (m, 1 H), 4.53-4.42 (m, 1 H), 4.33-4.24 (m, 1 H), 3.43-3.34 (m, 1 H), 3.25-3.21 (m, 3 H), 3.09-2.88 (m, 2 H), 2.84-2.76 (m, 1 H), 2.62 –2.56 (m, 6 H), 2.42-2.20 (m, 6 H), 2.08-2.06 (m, 1 H), 1.95-1.88 (m, 6 H), 1.84-1.63 (m, 6 H), 1.53-1.46 (m, 2 H), 0.90-0.84 (m, 3 H). HRMS *m/z* (M+H)$^+$ calcd: 700.3697, obsd: 700.3696.

Example 530

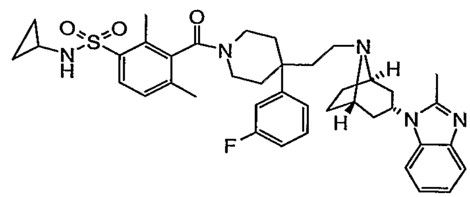
Preparation of 3-[(4-(3-fluorophenyl)-4-{2-[(1R, 5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)carbonyl]-N-isopropyl-2,4-dimethylbenzenesulfonamide



3-[(4-(3-Fluorophenyl)-4-{2-[(1*R*, 5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)carbonyl]-*N*-isopropyl-2,4-dimethylbenzenesulfonamide (8 mg, 12%) was obtained as solid from 3-(chlorosulfonyl)-2,6-dimethylbenzoic acid (50 mg, 0.2 mmol), isopropylamine (19 μL, 0.22 mmol), 1-((1*R*,5*S*)-8-{2-[4-(3-fluorophenyl)piperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1*H*-benzimidazole dihydrochloride (52 mg, 0.1 mmol) and HATU (38mg, 0.1 mmol) following the procedure outlined in example 473. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94-7.92 (m, 1 H), 7.66 (d, J=7.1 Hz, 1 H), 7.36 (q, J=7.7 HZ, 1 H), 7.30-7.29 (m, 1 H), 7.21-7.14 (m, 3 H), 7.06 (d, J=7.9 HZ, 1 H), 6.99-6.95 (m, 2 H), 4.64-4.60 (m, 1 H), 4.34-4.24 (m, 2 H), 3.46-3.35 (m, 2 H), 3.25-3.20 (m, 3 H), 3.06-2.95 (m, 1 H), 2..61 (s, 3 H), 2.58 (s, 3 H), 2.44-2.30 (m, 3 H), 2.20 (s, 3 H), 2.08-2.06 (m, 1 H), 1.95-1.86 (m, 6 H), 1.85-1.64 (m, 6 H), 1.19-1.15 (m, 3H), 1.05-1.01 (m, 3 H). HRMS *m/z* $(M+H)^+$ calcd: 700.3697, obsd: 700.3711.

Example 531

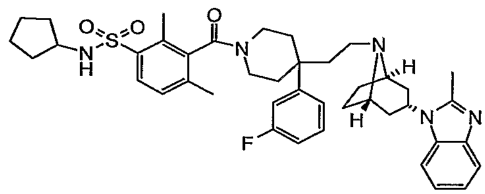
Preparation of N-cyclopropyl-3-[(4-(3-fluorophenyl)-4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)carbonyl]-2,4-dimethylbenzenesulfonamide



N-Cyclopropyl-3-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo [3.2.1]oct-8-yl]ethyl}piperidin-1-yl)carbonyl]-2,4-dimethylbenzenesulfonamide (12 mg, 17%) was obtained as solid from 3-(chlorosulfonyl)-2,6-dimethylbenzoic acid (50 mg, 0.2 mmol), cyclopropylamine (15μL, 0.22 mmol), 1-((1*R*,5*S*)-8-{2-[4-(3-fluorophenyl)piperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1*H*-benzimidazole dihydrochloride (52 mg, 0.1 mmol) and HATU (38mg, 0.1 mmol) following the procedure outlined in example 473. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, J=8.0 Hz, 1 H), 7.66 (d, J=8.0 Hz, 1 H), 7.38-7.34 (m, 1 H), 7.31-7.29 (m, 1 H), 7.21-7.13 (m, 3 H), 7.06 (d, J=8.0 Hz, 1 H), 6.99-6.95 (m, 2 H), 5.29-5.14 (m, 1 H), 4.61(br, 1 H), 4.32-4.29 (m, 1 H), 3.60-3.37 (m, 2 H), 3.24-3.20 (m, 3 H), 3.06-3.01 (m, 2 H), 2.60 –2.57 (m, 6 H), 2.40-2.30 (m, 3 H), 2.21 (s, 3 H), 2.08-2.06 (m, 1 H), 1.94-1.81 (m, 9 H), 1.69-1.63 (m, 3 H), 0.60-0.53 (m, 4 H). HRMS *m/z* $(M+H)^+$ calcd: 698.3540, obsd: 698.3567.

Example 532

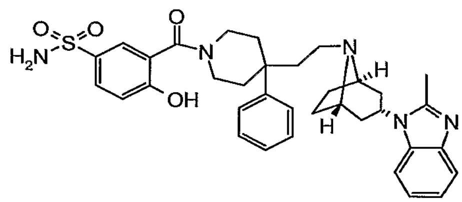
Preparation of N-cyclopentyl-3-[(4-(3-fluorophenyl)-4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)carbonyl]-2,4-dimethylbenzenesulfonamide



N-Cyclopentyl-3-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo [3.2.1]oct-8-yl]ethyl}piperidin-1-yl)carbonyl]-2,4-dimethylbenzenesulfonamide (24 mg, 33%) was obtained as solid from 3-[(cyclopentyl amino)sulfonyl]-2,6-dimethyl benzoic acid (30 mg, 0.1 mmol), 1-((1*R*,5*S*)-8-{2-[4-(3-fluorophenyl)piperidin-4-yl]ethyl}-8-azabicyclo[3.2.1] oct-3-yl)-2-methyl-1*H*-benzimidazole dihydrochloride (52 mg, 0.1 mmol) and HATU (38mg, 0.1 mmol) following the procedure outlined in example 5. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93-7.91 (m, 1 H), 7.67-7.64 (m, 1 H), 7.36 (q. J=8.0 Hz, 1 H), 7.30-7.28 (m, 1 H), 7.21-7.12 (m, 3H), 7.07-7.05 (m, 1 H), 6.99-6.95 (m, 2 H), 4.63-4.53 (m, 2 H), 4.31-4.28 (m, 1 H), 3.59-3.50 (m, 1 H), 3.44-3.34 (m, 1 H), 3.24 (br, 3 H), 3.08 –3.00 (m, 1 H), 2.61 (s, 3/2H, rotamer), 2.57 (s, 3/2 H, rotamer), 2.56 (s, 3/2 H, rotamer), 2.41 (s, 3/2 H, rotamer), 2.39 (s, 3/2 H, rotamer), 2.36-2.34 (m, 3 H), 2.20 (s, 3/2 H, rotamer), 2.08 (br, 1 H), 1.95-1.76 (m, 10 H), 1.69-1.56 (m, 5 H), 1.52-1.45 (m, 3 H), 1.32-1.27 (m, 1 H). HRMS *m/z* $(M+H)^+$ calcd: 726.3853, obsd: 726.3824.

Example 533

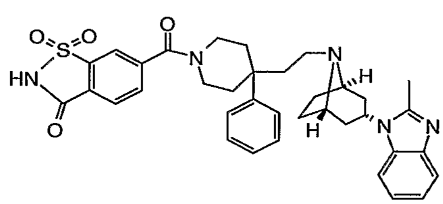
Preparation of 4-hydroxy-3-[(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]benzene sulfonamide



4-Hydroxy-3-[(4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]benzenesulfonamide (20 mg) was obtained as solid from 5-(aminosulfonyl)-2-hydroxybenzoic acid (43 mg, 0.2 mmol), 2-methyl-1-{(1*R*,5*S*)-8-[2-(4-phenylpiperidin-4-yl)ethyl]-8-aza bicyclo[3.2.1]oct-3-yl}-1*H*-benzimidazole (100mg, 0.2 mmol) and HATU (76mg, 0.2 mmol) following the procedure outlined in example 5. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.66 (s, 1 H), 7.74 (s, 1 H), 7.65 (dd, J=2.4, 8.2 Hz, 1 H), 7.54 (d, J=2.2 Hz, 1 H), 7.49-7.47 (m, 1 H), 7.38 (br, 5 H), 7.22-7.10 (m, 5 H), 6.96 (d, 8.6 Hz, 1 H), 4.48 (br, 1 H), 3.90 (br, 1 H), 3.24 (br, 1 H), 3.09-3.03 (m, 4 H), 2.47-2.45 (m, 6 H), 2.09 (br, 5 H), 1.81 (br, 6 H), 1.57 (br, 1 H). HRMS *m/z* $(M+H)^+$ calcd: 628.2958, obsd: 628.2958.

Example 534

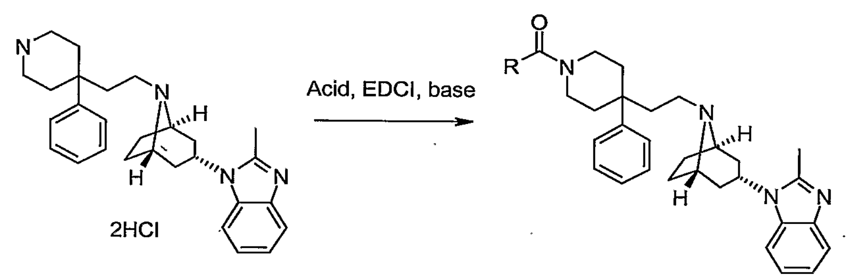
Preparation of 6-[(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]-1,2-benzisothiazol-3(2H)-one 1,1-dioxide



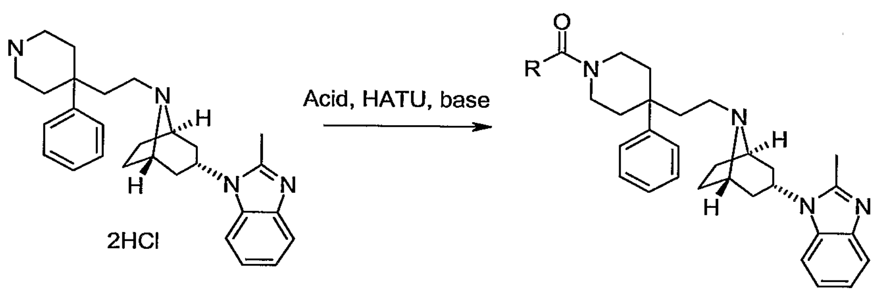
6-[(4-{2-[(1*R*, 5*S*)-3-(2-Methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]-1,2-

benzisothiazol-3(2*H*)-one 1,1-dioxide (78mg, 61%) was obtained as solid from 3-oxo-2,3-dihydro-1,2-benzisothiazole-6-carboxylic acid 1,1-dioxide (46 mg, 0.2 mmol), 2-methyl-1-{(1*R*, 5*S*)-8-[2-(4-phenylpiperidin-4-yl)ethyl]-8-azabicyclo [3.2.1]oct-3-yl}-1*H*-benzimidazole (100mg, 0.2 mmol) and HATU (76mg, 0.2 mmol) following the procedure outlined in example 5. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.63-7.61 (m, 2 H), 7.57-7.54 (m, 1 H), 7.50-7.47 (m, 1 H), 7.44-7.33 (m, 5 H), 7.25-7.20 (m, 1 H), 7.15-7.07 (m, 3, H), 4.69-4.63 (m, 1 H), 3.93(br, 1 H), 3.47 (br, 3 H), 3.39-3.30 (m, 1 H), 2.48 (s, 3 H), 2.43-2.38 (m, 4 H), 2.27-2.20 (m, 4 H), 1.97-1.78 (m, 7 H), 1.78-1.66 (m, 2 H). HRMS *m/z* (M+H)$^+$ calcd: 638.2801, obsd: 638.2796.

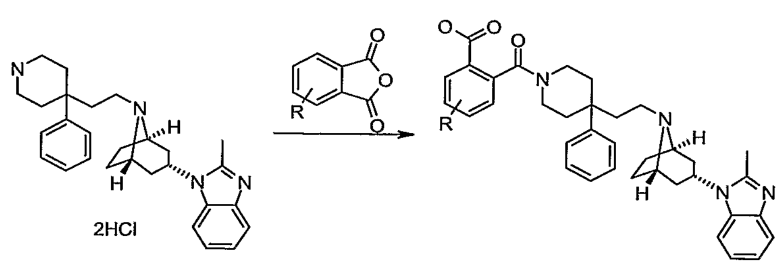
Synthesis of amides via EDCI coupling - Method P



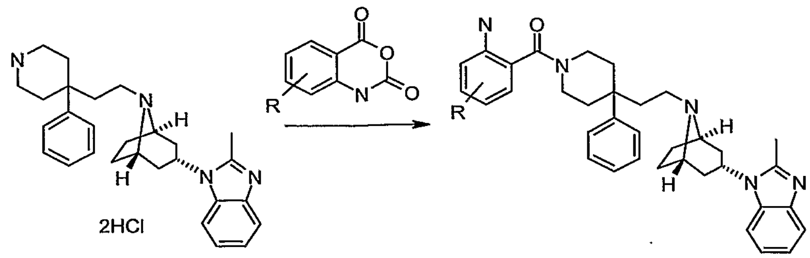
Synthesis of amides via HATU-mediated coupling - Method A



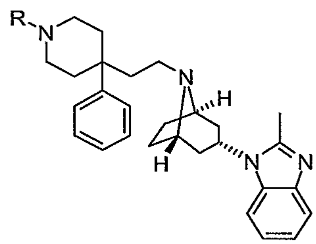
Synthesis of amides via anhydride - Method B

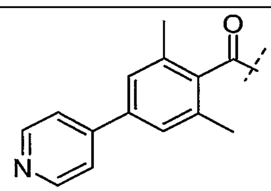
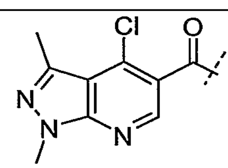
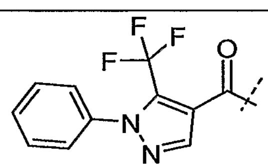
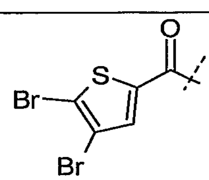


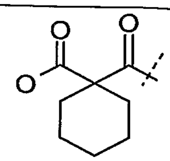
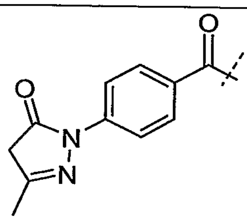
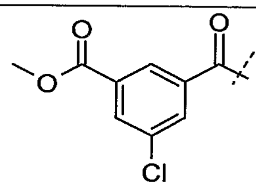
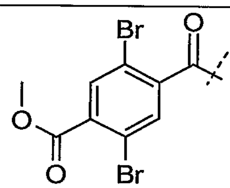
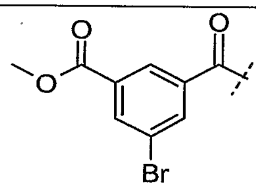
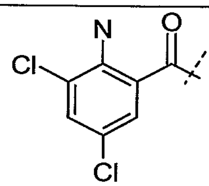
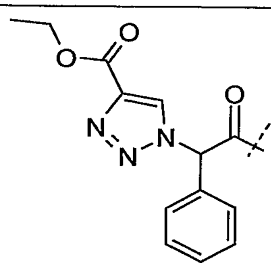
Synthesis of amides via Isatoic Anhydride opening - Method U

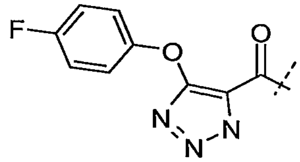
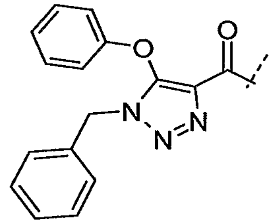
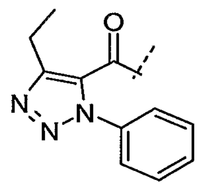
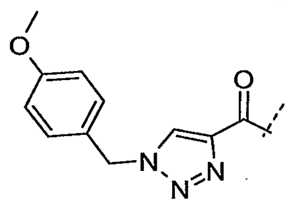
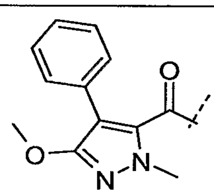
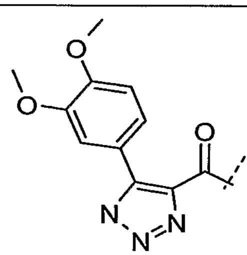
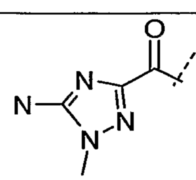


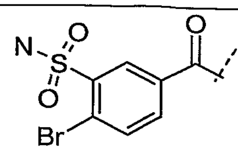
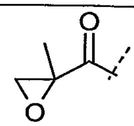
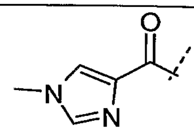
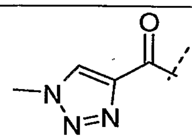
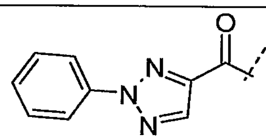
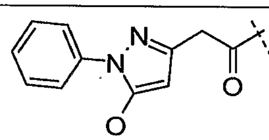
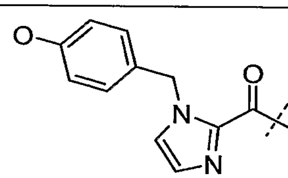
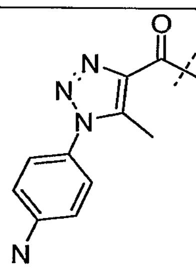
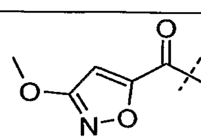
The following table includes compounds of the present invention that were prepared by the methods depicted above.

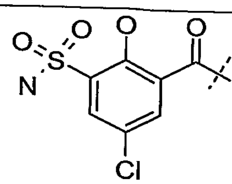
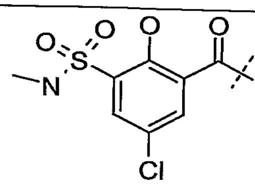
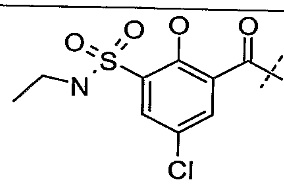
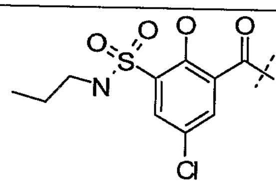
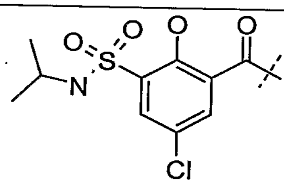
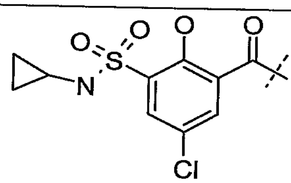
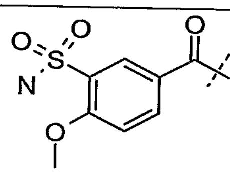
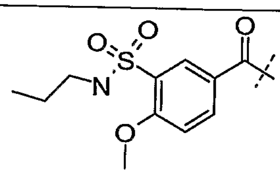


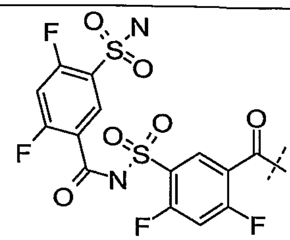
Example	R	ES-LCMS	Ion	Method	Notes
535		637	M+H	P	1
536		635	M+H	A	
537		666	M+H	A	
538		694	M+H	A	

539		582	M+H	A	2
540		628	M+H	A	
541		628	M+H	A	3
542		746	M+H	A	3
543		668	M+H	A	3
544		615	M+H	U	
545		685	M+H	A	4

546		633	M+H	A	5
547		705	M+H	A	5
548		627	M+H	A	5
549		643	M+H	A	5
550		642	M+H	A	6
551		659	M+H	A	5
552		552	M+H	A	7

553		689	M+H	A	8
554		512	M+H	A	
555		536	M+H	A	
556		537	M+H	A	9
557		599	M+H	A	9
558		628	M+H	A	6
559		628	M+H	A	10
560		628	M+H	A	5
561		553	M+H	A	11

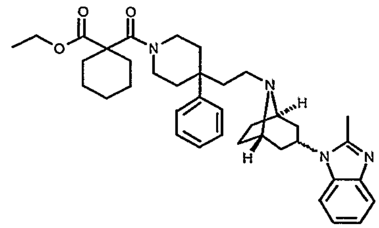
562		661	M+H	A	8
563		675	M+H	A	8
564		689	M+H	A	8
565		703	M+H	A	8
566		703	M+H	A	8
567		701	M+H	A	8
568		641	M+H	A	8
569		683	M+H	A	8

570		866	M+H	A	8

Notes:

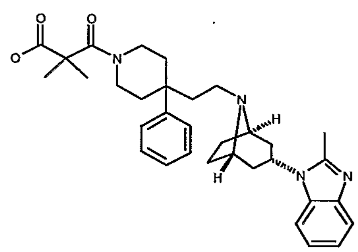
1. Compound was synthesized according to WO 00/66558, Schering Corporation, 2000.
2. Compound was synthesized according to procedure outlined for example 572.
3. Compound was synthesized according to the literature procedure described by M. H. Chen et al., *Org. Prep. Proced. Int.*, 2000, v32, pp. 381-384.
4. Compound was synthesized according to the literature procedure described in *J. Heterocycl. Chem.* 26(5), 1461-8 (1989).
5. Compound was synthesized according to the literature procedure described in *J. Chem. Res. Synop.* 12, 400-1 (1984).
6. Compound was synthesized according to the literature procedure described in *Chem. Ber.*, 109(1), 268-73 (1976).
7. Compound was synthesized according to the procedure described in EP 0016565A1, 1980.
8. Compound was synthesized according to procedure outlined for example 572.
9. Compound was synthesized according to the literature procedure described in *J. Org. Chem.*, 41(6), 1041-51 (1976).
10. Compound was synthesized according to the literature procedure described in *J. Med. Chem.*, 33(2), 781-9 (1990).
11. Compound was synthesized according to the literature procedure described in *Bioorganic & Medicinal Chemistry Letters*, 9(18), 2679-2684 (1999).

Example 571



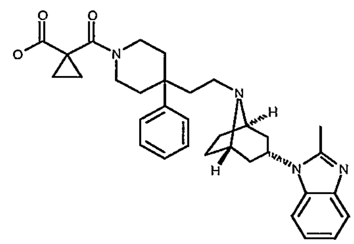
Ethyl 1-[(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenyl piperidin-1-yl)carbonyl]cyclohexanecarboxylate was synthesized via EDCI-HOBt acylation method P. ^{1}H NMR (300MHz, $CDCl_3$) δ 7.66(d, 1H), 7.43-7.12(m, 8H), 4.61(m, 1H), 4.22-4.09(m, 2H), 3.65(m, 1H), 3.33-3.05(m, 4H), 2.88(m, 1H), 2.58(s, 3H), 2.46-2.11(m, 4H), 2.05(s, 1H),2.00-1.83(m, 12H), 1.63-1.52(m, 6H), 1.50-1.37(m, 2H),1.07-1.32 (m, 4H). HRMS $C_{38}H_{50}N_4O_3$ m/z 611.3961 $(M+H)_{Cal.}$, 611.3973 $(M+H)_{Obs}$.

Example 572



2,2-Dimethyl-3-(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)-3-oxopropanoic acid was prepared by treating title compound from example 628 with NaOH. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.75 (d, 1H), 7.43-7.12 (m, 8H), 4.68 (m, 1H), 4.07 (m, 1H), 3.69 (m, 1H), 3.30-3.14 (m, 2H), 2.70-2.58 (m, 3H), 2.20 (m, 2H), 2.05-1.73 (m, 7H), 1.50-1.07 (m, 12H), 1.02-0.74 (m, 3H). HRMS $C_{33}H_{42}N_4O_3$ m/z 543.3335 $(M+H)_{Cal}$. 543.3337 $(M+H)_{Obs}$.

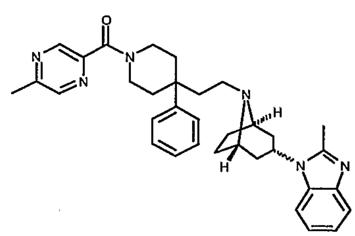
Example 573



1-[(4-{2-[(1R,5S)-3-(2-Methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]cyclopropanecarboxylic acid was prepared by treating title compound from example 573 with NaOH. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.66 (d, 1H), 7.40-7.10 (m, 8H), 4.62 (m, 1H), 4.14 (m, 1H), 3.25 (m, 2H), 3.08 (m, 2H), 2.58 (s, 3H), 2.43-2.19(m, 3H), 2.05-1.78(m, 8H), 1.27(s, 6H) 0.92-0.78(m, 2H). HRMS $C_{33}H_{40}N_4O_3$ m/z 541.3179 $(M+H)_{Cal.}$, 541.3163 $(M+H)_{Obs.}$.

Example 574

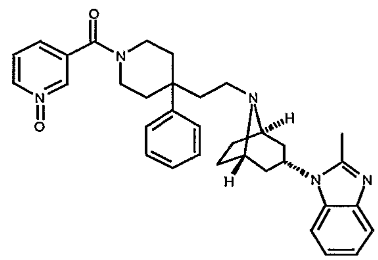
2-Methyl-1-[(1R,5S)-8-(2-{1-[(5-methylpyrazin-2-yl)carbonyl]-4-phenylpiperidin-4-yl}ethyl)-8-azabicyclo[3.2.1]oct-3-yl]-1H-benzimidazole



Method A (HATU). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.78(s, 1H), 8.41(s, 1H), 7.67(d, 1H), 7.45-7.09(m, 8H), 4.61(m, 1H), 4.25(m, 1H), 3.75(m, 1H), 3.42-3.19(m, 4H), 2.62(s, 3H), 2.57(s, 3H), 2.40-2.19(m, 4H), 2.00-1.79(m, 10H), 1.63(m, 2H). ES-LCMS m/z 548(M+H).

Example 575

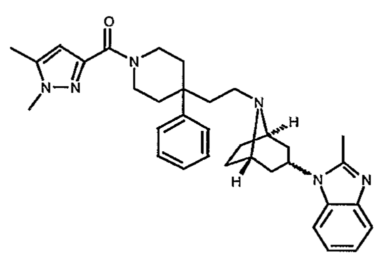
2-Methyl-1-[(1R,5S)-8-(2-{1-[(1-oxidopyridin-3-yl)carbonyl]-4-phenylpiperidin-4-yl}ethyl)-8-azabicyclo[3.2.1]oct-3-yl]-1H-benzimidazole



Method A (HATU). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.23 (d, 1H), 7.68 (d, 1H), 7.45-7.10 (m, 11H), 4.61 (m, 1H), 4.24 (m, 1H), 3.53 (m, 1H), 3.30-3.18 (m, 4H), 2.58 (s, 3H), 2.40-2.29 (m, 3H), 2.01-1.80 (m, 9H), 1.65 (m, 4H). ES-LCMS m/z 549(M+H).

Example 576

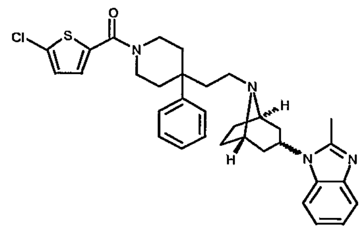
1-[(1R,5S)-8-(2-{1-[(1,5-dimethyl-1H-pyrazol-3-yl)carbonyl]-4-phenylpiperidin-4-yl}ethyl)-8-azabicyclo[3.2.1]oct-3-yl]-2-methyl-1H-benzimidazole



Method A (HATU). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.68 (d, 1H), 7.45-7.10 (m, 8H), 6.36 (s, 1H), 4.63 (m, 1H), 4.30-4.10 (m, 2H), 3.79 (s, 3H), 3.62 (m, 1H), 3.40-3.21 (m, 3H), 2.57 (s, 3H), 2.45-2.20 (m, 7H), 2.02-1.78 (m, 10H), 1.64-1.57 (m, 2H). ES-LCMS m/z 550(M+H).

Example 577

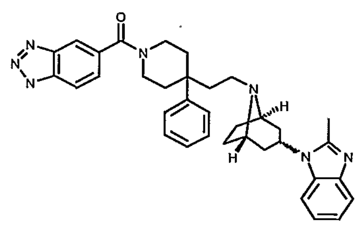
1-[(1R,5S)-8-(2-{1-[(5-chlorothien-2-yl)carbonyl]-4-phenylpiperidin-4-yl}ethyl)-8-azabicyclo[3.2.1]oct-3-yl]-2-methyl-1H-benzimidazole



Method A (HATU). ^1H NMR (300 MHz, $CDCl_3$) δ 7.68 (d, 1H), 7.45-7.01 (m, 9H), 6.86 (d, 1H), 4.61 (m, 1H), 4.15-3.97 (m, 2H), 3.41 (m, 2H), 3.25 (m, 2H), 2.57 (s, 3H), 2.45-2.25 (m, 4H), 2.00-1.77 (m, 10H), 1.61-1.58 (m, 2H). ES-LCMS m/z 572(M+H).

Example 578

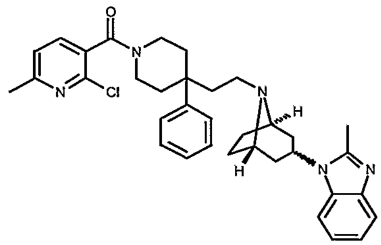
5-[(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]-1H-1,2,3-benzotriazole



Method A (HATU). ^1H NMR (300 MHz, $CDCl_3$) δ 7.94 (s, 1H), 7.84 (d, 1H), 7.69 (d, 1H), 7.48-7.14(m,10H), 4.64 (m, 1H), 4.27 (m, 1H), 3.61 (m, 1H), 3.49-3.22 (m, 4H), 2.54 (s, 3H), 2.45-2.30 (m, 3H), 2.22 (m, 1H), 2.05-1.73 (m, 10H), 1.68-1.57 (m, 2H). ES-LCMS m/z 573(M+H).

Example 579

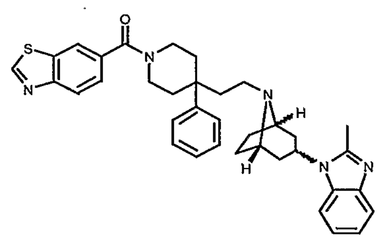
1-[(1R,5S)-8-(2-{1-[(2-chloro-6-methylpyridin-3-yl)carbonyl]-4-phenylpiperidin-4-yl}ethyl)-8-azabicyclo[3.2.1]oct-3-yl]-2-methyl-1H-benzimidazole



Method A (HATU). ^1H NMR (300 MHz, $CDCl_3$) δ 7.70-7.55 (m, 1H), 7.47-7.08 (m, 10H), 4.61 (m, 1H), 4.23 (m, 1H), 3.49-3.17 (m, 5H), 2.57 (s, 6H), 2.45-2.29 (m, 3H), 2.13 (m, 1H), 2.02-1.78 (m, 10H), 1.68-1.56 (m, 2H). ES-LCMS m/z 581(M+H)

Example 580

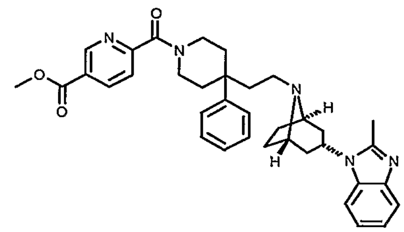
6-[(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]-1,3-benzothiazole



Method A (HATU). ^1H NMR (300 MHz, $CDCl_3$) δ 9.08 (s, 1H), 8.20 (d, 1H), 8.03 (s, 1H), 7.69 (d, 1H), 7.55 (d, 1H), 7.41-7.09 (m, 8H), 4.61 (m, 1H), 4.23 (m, 1H), 3.62 (m, 1H), 3.48-3.17 (m, 4H), 2.55 (s, 3H), 2.45-2.28 (m, 3H), 2.25-2.09 (m, 2H), 2.01-1.78 (m, 9H), 1.63 (d, 2H). ES-LCMS m/z 589(M+H).

Example 581

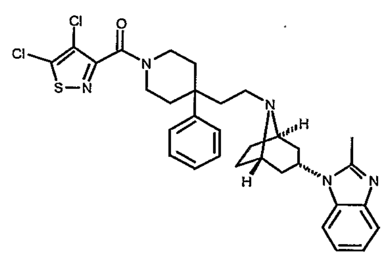
methyl 6-[(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]nicotinate



Method A (HATU). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.19 (s, 1H), 8.38 (d, 1H), 7.65 (d, 1H), 7.45-7.09 (m, 8H), 4.61 (m, 1H), 4.21 (m, 1H), 3.98 (s, 3H), 3.64 (m, 1H), 3.48-3.21 (m, 4H), 2.57 (s, 3H), 2.48-2.29 (m, 3H), 2.25-2.15 (m, 1H), 2.02-1.79 (m, 10H), 1.62-1.55 (m, 2H). ES-LCMS m/z 591(M+H).

Example 582

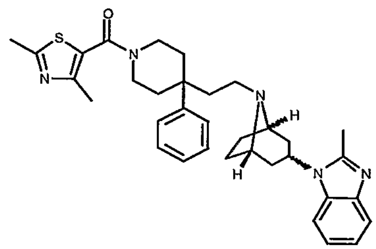
1-[(1R,5S)-8-(2-{1-[(4,5-dichloroisothiazol-3-yl)carbonyl]-4-phenylpiperidin-4-yl}ethyl)-8-azabicyclo[3.2.1]oct-3-yl]-2-methyl-1H-benzimidazole



Method A (HATU). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.68 (d, 1H), 7.43-7.09 (m, 8H), 4.65 (m, 1H), 4.30-4.13 (m, 1H), 3.60-3.17 (m, 5H), 2.58 (s, 3H), 2.46-2.19 (m, 4H), 2.05-1.81 (m, 10H), 1.69-1.59 (m, 2H). ES-LCMS m/z 607(M+H).

Example 583

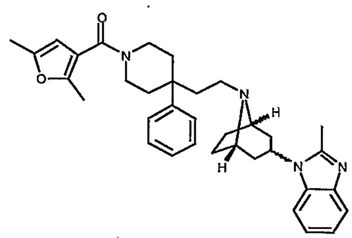
1-[(1R,5S)-8-(2-{1-[(2,4-dimethyl-1,3-thiazol-5-yl)carbonyl]-4-phenylpiperidin-4-yl}ethyl)-8-azabicyclo[3.2.1]oct-3-yl]-2-methyl-1H-benzimidazole



Method A (HATU). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.65 (d, 1H), 7.46-7.18 (m, 8H), 4.61 (m, 1H), 3.98 (m, 1H), 3.42-3.19 (m, 4H), 2.67 (s, 3H), 2.56 (s, 3H), 2.41-2.19 (m, 7H), 2.05-1.75 (m, 10H), 1.70-1.55 (m, 2H). ES-LCMS m/z 567(M+H).

Example 584

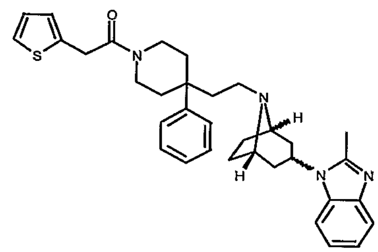
1-((1R,5S)-8-{2-[1-(2,5-dimethyl-3-furoyl)-4-phenylpiperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1H-benzimidazole



Method A (HATU). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.68 (d, 1H), 7.42-7.11 (m, 8H), 5.91 (s, 1H), 4.61 (m, 1H), 4.06 (m, 1H), 3.76 (m, 1H), 3.40-3.18 (m, 4H), 2.57 (s, 3H), 2.44-2.33 (m, 4H), 2.31 (s, 3H), 2.24 (s, 3H), 2.00-1.72 (m, 10H), 1.62-1.53 (m, 2H). ES-LCMS m/z 550(M+H).

Example 585

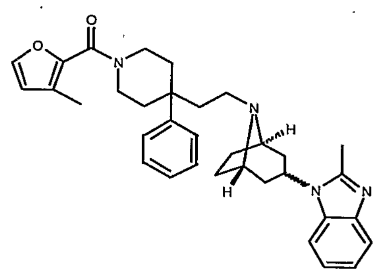
2-methyl-1-((1R,5S)-8-{2-[4-phenyl-1-(thien-2-ylacetyl) piperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-1H-benzimidazole



Method A (HATU). [1]H NMR (300 MHz, $CDCl_3$) δ 7.71 (d, 1H), 7.43-7.09 (m, 9H), 7.01-6.83 (m, 2H), 4.75 (m,1H), 4.10-3.97 (m, 1H), 3.90 (s, 2H), 3.84 (s, 1H), 3.75-3.59 (m, 4H), 2.54 (s, 3H), 2.52-2.36 (m, 1H), 2.25-1.57 (m, 14H). ES-LCMS m/z 552(M+H).

Example 586

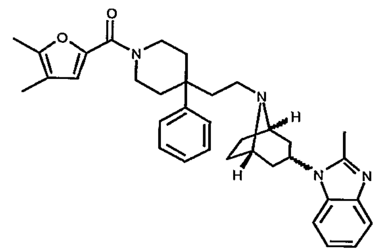
2-methyl-1-((1R,5S)-8-{2-[1-(3-methyl-2-furoyl)-4-phenylpiperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-1H-benzimidazole



Method A (HATU). [1]H NMR (300 MHz, $CDCl_3$) δ 7.66 (d, 1H), 7.43-7.09 (m, 9H), 6.32 (s, 1H), 4.63(m,1H), 3.98 (m, 1H), 3.48-3.20 (m, 4H), 2.58 (s, 3H), 2.48-2.20 (m, 7H), 2.02-1.78 (m, 10H), 1.70-1.55 (m, 2H). ES-LCMS m/z 536(M+H).

Example 587

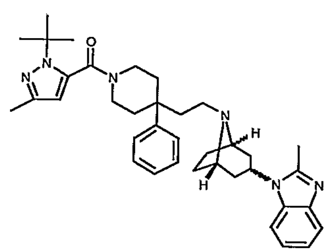
1-((1R,5S)-8-{2-[1-(4,5-dimethyl-2-furoyl)-4-phenylpiperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1H-benzimidazole



Method A (HATU). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.68 (d, 1H), 7.44-7.13 (m, 8H), 6.73 (s, 1H), 4.64(m,1H), 4.20-4.07 (m, 2H), 3.55-3.21 (m, 4H), 2.58 (s, 3H), 2.48-2.21 (m, 7H), 2.03-1.80 (m, 13H), 1.70-1.59 (m, 2H). ES-LCMS m/z 550(M+H).

Example 588

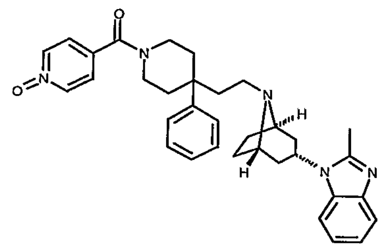
1-[(1R,5S)-8-(2-{1-[(1-tert-butyl-3-methyl-1H-pyrazol-5-yl)carbonyl]-4-phenylpiperidin-4-yl}ethyl)-8-azabicyclo[3.2.1]oct-3-yl]-2-methyl-1H-benzimidazole



Method A (HATU). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.66 (d, 1H), 7.46-7.13 (m, 8H), 5.95 (s, 1H), 4.63 (m, 1H), 4.20-4.13 (m, 1H), 3.62-3.48 (m, 1H), 3.41-3.13 (m, 4H), 2.58 (s, 3H), 2.48-2.28 (m, 3H), 2.26 (s, 1H), 2.24-2.10 (m, 1H), 2.00-1.65 (m, 12H), 1.59 (s, 10H). ES-LCMS m/z 592(M+H).

Example 589

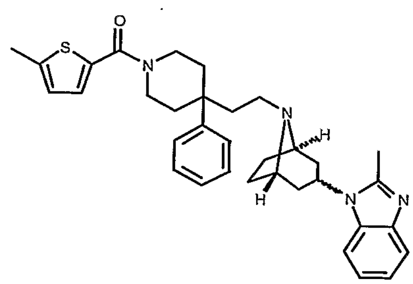
2-methyl-1-((1R,5S)-8-{2-[1-(1-oxidoisonicotinoyl)-4-phenylpiperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-1H-benzimidazole



Method A (HATU). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.25 (d, 2H), 8.18 (d, 1H), 7.42-7.12 (m, 10H), 4.63 (m, 1H), 3.39-3.20 (m, 4H), 2.58 (s, 3H), 2.41-2.30 (m, 3H), 1.97-1.77 (m, 10H), 1.68-1.49 (m, 5H). ES-LCMS m/z 549(M+H).

Example 590

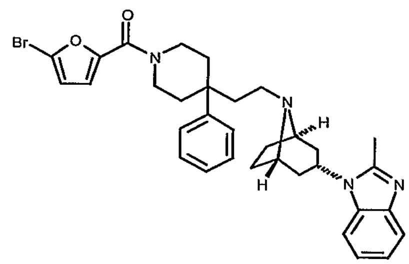
2-methyl-1-[(1R,5S)-8-(2-{1-[(5-methylthien-2-yl)carbonyl]-4-phenylpiperidin-4-yl}ethyl)-8-azabicyclo[3.2.1]oct-3-yl]-1H-benzimidazole



Method A (HATU). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.68 (d, 1H), 7.45-7.06 (m, 9H), 6.69 (m, 1H), 4.64 (m, 1H), 4.19-4.00 (m, 2H), 3.44 (m, 2H), 3.30 (m, 2H), 2.58 (s, 3H), 2.51 (s, 3H), 2.48-2.23 (m, 4H), 2.04-1.81 (m, 10H), 1.70-1.60 (m, 2H). ES-LCMS m/z 552(M+H).

Example 591

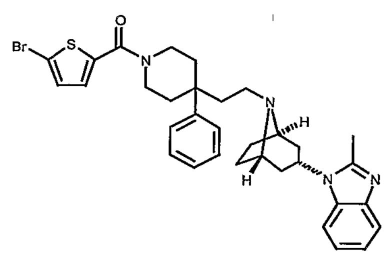
1-((1R,5S)-8-{2-[1-(5-bromo-2-furoyl)-4-phenylpiperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1H-benzimidazole



Method A (HATU). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.69 (d, 1H), 7.47-7.13 (m, 8H), 6.96 (d, 1H), 6.43 (d, 1H), 4.66 (m, 1H), 4.20-4.07 (m, 2H), 3.52-3.22 (m, 4H), 2.59 (s, 3H), 2.49-2.24 (m, 4H), 2.04-1.81 (m, 10H), 1.70-1.60 (m, 2H). ES-LCMS m/z 600(M+H).

Example 592

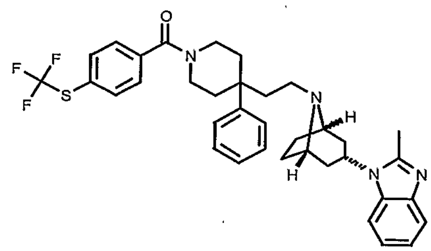
1-[(1R,5S)-8-(2-{1-[(5-bromothien-2-yl)carbonyl]-4-phenylpiperidin-4-yl}ethyl)-8-azabicyclo[3.2.1]oct-3-yl]-2-methyl-1H-benzimidazole



Method A (HATU). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.66 (d, 1H), 7.48-7.13 (m, 9H), 7.07-6.95 (m, 1H), 4.64 (m, 1H), 4.10-3.94 (m, 2H), 3.53-3.21 (m, 4H), 2.58 (s, 3H), 2.46-2.25 (m, 4H), 2.04-1.79 (m, 10H), 1.71-1.57 (m, 2H). ES-LCMS m/z 616(M+H).

Example 593

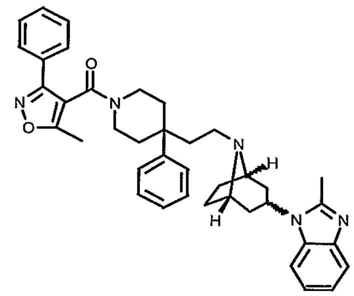
2-methyl-1-{(1R,5S)-8-[2-(4-phenyl-1-{4-[(trifluoromethyl)thio]benzoyl}piperidin-4-yl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1H-benzimidazole



Method A (HATU). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.80-7.62 (m, 3H), 7.50-7.11 (m, 11H), 4.63 (m, 1H), 4.25-4.13 (m, 1H), 3.60-3.17 (m, 4H), 2.57 (s, 1H), 2.44-2.29 (m, 3H), 2.20-2.08 (m, 1H), 2.02-1.70 (m, 10H), 1.62-1.57 (m, 2H). ES-LCMS m/z 632(M+H).

Example 594

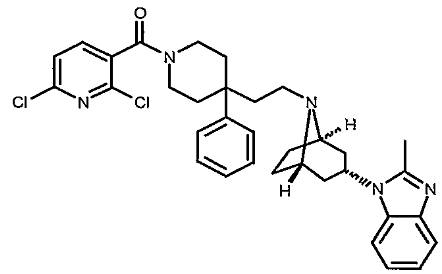
2-methyl-1-[(1R,5S)-8-(2-{1-[(5-methyl-3-phenylisoxazol-4-yl)carbonyl]-4-phenylpiperidin-4-yl}ethyl)-8-azabicyclo[3.2.1]oct-3-yl]-1H-benzimidazole



Method A (HATU). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.74-7.65 (m, 2H), 7.51-7.14 (m, 12H), 4.59 (m, 1H), 4.18 (m, 1H), 3.38-3.17 (m, 4H), 2.57 (s, 3H), 2.48 (s, 3H), 2.44-2.17 (m, 4H), 2.01-1.54 (m, 12H). ES-LCMS m/z 613(M+H).

Example 595

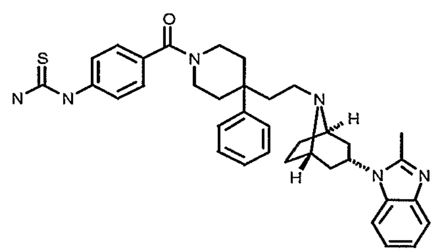
1-[(1R,5S)-8-(2-{1-[(2,6-dichloropyridin-3-yl)carbonyl]-4-phenylpiperidin-4-yl}ethyl)-8-azabicyclo[3.2.1]oct-3-yl]-2-methyl-1H-benzimidazole



Method A (HATU). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.74-7.60 (m, 2H), 7.54-7.05 (m, 9H), 4.61 (m, 1H), 4.23 (m, 1H), 3.45-3.02 (m, 5H), 2.56 (s, 3H), 2.47-2.09 (m, 4H), 2.00-1.75 (m, 8H), 1.70-1.53 (m, 2H), 1.28-1.20 (m, 2H). ES-LCMS m/z 601(M+H).

Example 596

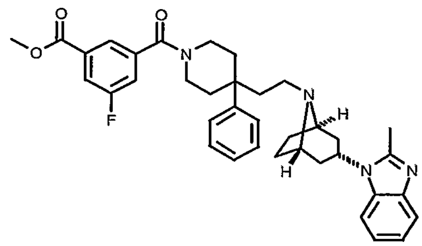
N-{4-[(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]phenyl}thiourea



Method A (HATU). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.95 (s, 1H), 7.67 (d, 1H), 7.45-7.06 (m, 10H), 6.35 (s, 1H), 4.61 (m, 1H), 4.20-4.09 (m, 1H), 3.71-3.51 (m, 1H), 3.48-3.16 (m, 4H), 2.56 (s, 3H), 2.46-2.13 (m, 4H), 2.04-1.55 (m, 13H), 1.27 (s, 2H). ES-LCMS m/z 606(M+H).

Example 597

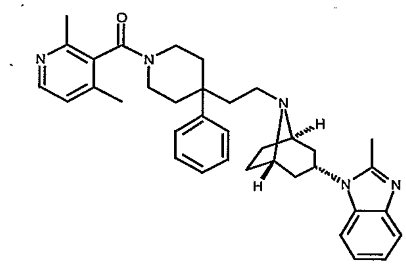
methyl 3-fluoro-5-[(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]benzoate



Method A (HATU). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.85-7.63 (m, 2H), 7.42-7.09 (m, 10H), 4.62 (m, 1H), 4.30-4.15 (m, 1H), 3.94 (s, 3H), 3.62-3.19 (m, 5H), 2.57 (s, 3H), 2.46-2.12 (m, 4H), 2.00-1.75 (m, 10H), 1.73-1.55 (m, 2H). ES-LCMS m/z 608(M+H).

Example 598

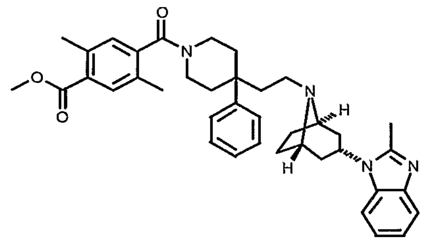
1-[(1R,5S)-8-(2-{1-[(2,4-dimethylpyridin-3-yl)carbonyl]-4-phenylpiperidin-4-yl}ethyl)-8-azabicyclo[3.2.1]oct-3-yl]-2-methyl-1H-benzimidazole



Method A (HATU). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.36 (d, 1H), 7.65 (d, 1H), 7.44-7.23 (m, 8H), 7.05-6.93 (m, 1H), 4.61 (m, 1H), 4.36-4.25 (m, 1H), 3.50-3.03 (m, 7H), 2.56 (m, 4H), 2.37 (m, 4H), 2.15 (s, 3H), 1.97-1.54 (m, 12H). ES-LCMS m/z 561(M+H).

Example 599

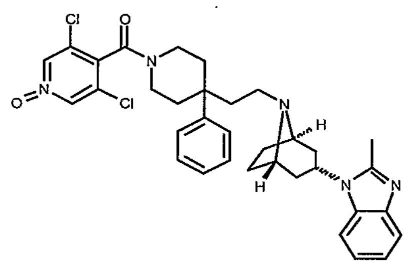
methyl 2,5-dimethyl-4-[(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]benzoate



Method A (HATU). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.83-7.60 (m, 2H), 7.50-7.08 (m, 9H), 4.62 (m, 1H), 4.30-4.11 (m, 1H), 3.91 (s, 2H), 3.42-3.08 (m, 6H), 2.94 (s, 3H), 2.81 (s, 3H), 2.57 (s, 3H), 2.40-2.14 (m, 4H), 2.05-1.75 (m, 10H), 2.20-1.57 (m, 2H). ES-LCMS m/z 618(M+H).

Example 600

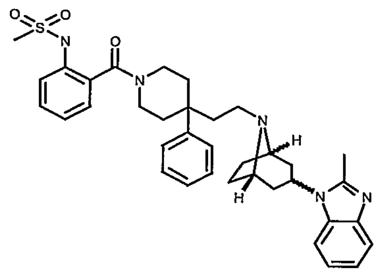
1-((1R,5S)-8-{2-[1-(3,5-dichloro-1-oxidoisonicotinoyl)-4-phenylpiperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1H-benzimidazole



Method A (HATU). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.23-8.10 (m, 1H), 7.70-7.61 (m, 1H), 7.45-7.08 (m, 9H), 4.61 (m, 1H), 4.35-4.24 (m, 1H), 2.58 (s, 3H), 2.48-2.22 (m, 4H), 2.04-1.77 (m, 10H), 1.70-1.57 (m, 2H). ES-LCMS m/z 617(M+H).

Example 601

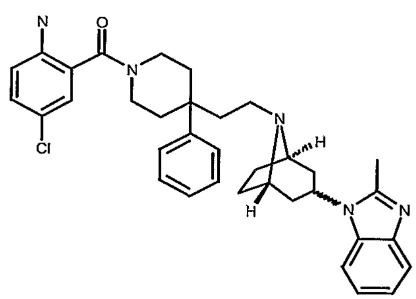
N-{2-[(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]phenyl}methanesulfonamide



Method A (HATU). ^{1}H NMR (300 MHz, methanol-d_4) δ 7.90-7.75 (m, 2H), 7.71-7.41 (m, 10H), 7.36-7.24 (m, 1H), 5.31 (m, 1H), 4.25-4.04 (m, 3H), 3.62-3.53 (m, 1H), 3.51-3.26 (m, 8H), 3.04-2.90 (m, 1H), 2.84 (s, 3H), 2.78-2.69 (m, 1H), 2.52-2.13 (m, 10H), 2.10-1.82 (m, 2H). ES-LCMS m/z 625(M+H).

Example 602

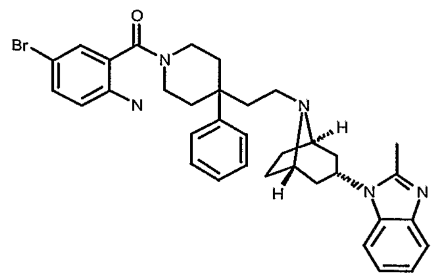
4-chloro-2-[(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]aniline



Method B (Anhydride). ^{1}H NMR (300 MHz, methanol-d_4) δ 7.81-7.73 (m, 2H), 7.63-7.57 (m, 2H), 7.46 (s, 1H), 7.31 (m, 1H), 7.20-7.03 (m, 2H), 6.79(d,1H), 5.27 (m, 1H), 4.11-4.03 (m, 2H), 3.30 (m, 6H), 2.97-2.86 (m, 2H), 2.82 (s, 3H), 2.77-2.70 (m, 2H), 2.45-2.11 (m, 10H), 1.95-1.83 (m, 2H). ES-LCMS m/z 581(M+H).

Example 603

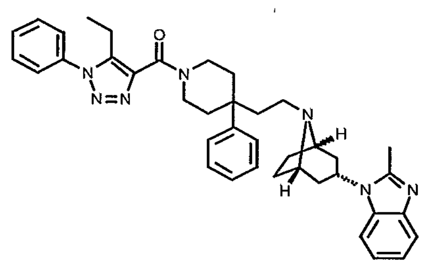
4-bromo-2-[(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]aniline



Method B (Anhydride). ^{1}H NMR (300 MHz, methanol-d_4) δ 8.08-7.93 (m, 2H), 7.85-7.72 (m, 2H), 7.64-7.55 (m, 2H), 7.50-7.42 (m, 4H), 7.34-7.27 (m, 1H), 6.80 (d, 1H), 5.31 (m, 1H), 4.14-4.00 (m, 1H), 3.38-3.27 (m, 6H), 2.98-2.87 (m, 2H), 2.86 (s, 3H), 2.83-2.71 (m, 2H), 2.44-2.14 (m, 10H), 2.00-1.85 (m, 2H). ES-LCMS m/z 625(M+H).

Example 604

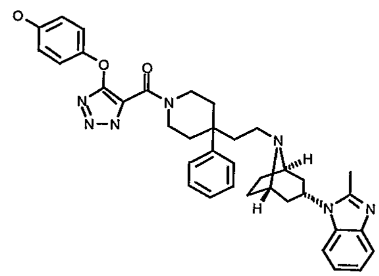
1-[(1R,5S)-8-(2-{1-[(5-ethyl-1-phenyl-1H-1,2,3-triazol-4-yl)carbonyl]-4-phenylpiperidin-4-yl}ethyl)-8-azabicyclo[3.2.1]oct-3-yl]-2-methyl-1H-benzimidazole



Method A (HATU). Acid precursor synthesized according to procedure outlined in *J. Chem. Res. Synop.*, 12, 400-1 (1984). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70-7.54 (m, 4H), 7.50-7.13 (m, 10H), 4.64 (m, 1H), 4.40-4.35 (m, 1H), 4.28-4.15 (m, 1H), 3.82-3.65 (m, 1H), 3.48-3.22 (m, 4H), 3.00-2.85 (m, 2H), 2.46-2.30 (m, 4H), 2.04-1.78 (m, 13H), 1.68-1.57 (m, 2H), 1.18-1.05 (m, 3H). ES-LCMS m/z 627(M+H).

Example 605

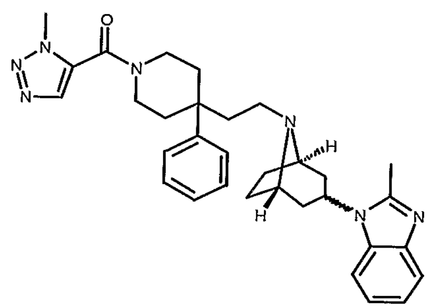
4-({5-[(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]-1H-1,2,3-triazol-4-yl}oxy)phenol



Method A (HATU). Acid precursor synthesized according to procedure outlined in *J. Chem. Res. Synop.*, 12, 400-1 (1984). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (d, 1H), 7.58-7.11 (m, 10H), 6.92-6.88 (m, 1H), 6.75-6.69 (m, 1H), 4.76 (m, 1H), 4.20-3.95 (m, 2H), 3.52-3.21 (m, 4H), 2.52-2.29 (m, 6H), 2.19-1.55 (m, 12H), 1.25 (s, 2H). ES-LCMS m/z 631 (M+H).

Example 606

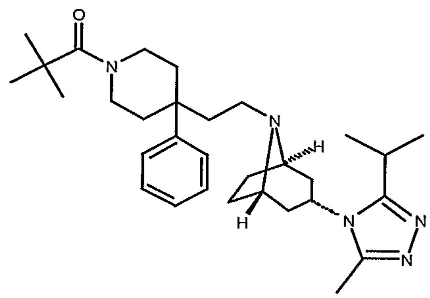
2-methyl-1-[(1R,5S)-8-(2-{1-[(1-methyl-1H-1,2,3-triazol-5-yl)carbonyl]-4-phenylpiperidin-4-yl}ethyl)-8-azabicyclo[3.2.1]oct-3-yl]-1H-benzimidazole



Method A (HATU). Acid precursor synthesized according to procedure outlined in *J. Org. Chem.* 41(6), 1041-51 (1976). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.75-7.62 (m, 2H), 7.46-7.11 (m, 8H), 4.67-4.53 (m, 1H), 4.16 (s, 3H), 3.85-3.71 (m, 1H), 3.46-3.18 (m, H), 2.45-2.22 (m, 4H), 1.98-1.58 (m, 16H). ES-LCMS m/z 537(M+H).

Example 607

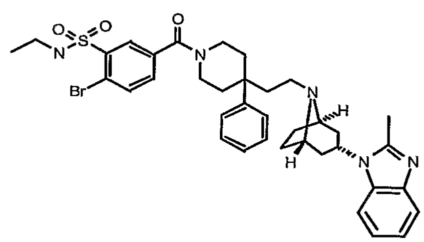
(1R,5S)-8-{2-[1-(2,2-dimethylpropanoyl)-4-phenylpiperidin-4-yl]ethyl}-3-(3-isopropyl-5-methyl-4H-1,2,4-triazol-4-yl)-8-azabicyclo[3.2.1]octane



Method A (HATU). Amine portion synthesized according to the procedure described in WO01109106A2, Pfizer Corp. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44-7.20 (m, 5H), 4.53 (m, 1H), 3.96-3.88 (m, 2H), 3.35-2.89 (m, 8H), 2.44 (s, 3H), 2.22-2.15 (m, 2H), 2.01-1.71 (m, 8H), 1.59-1.49 (m, 4H), 1.36 (d, 5H), 1.29 (s, 9H). ES-LCMS m/z 505(M+H).

Example 608

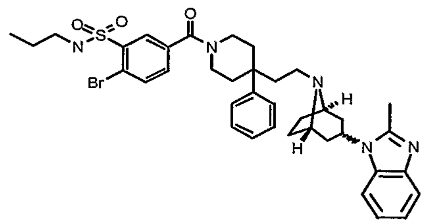
2-bromo-N-ethyl-5-[(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]benzenesulfonamide



Method A (HATU). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.14 (s, 1H), 7.80 (d, 1H), 7.68 (d, 1H), 7.48-7.15 (m, 9H), 5.19 (m, 1H), 4.63 (m, 1H), 4.24 (m, 1H), 3.57-3.49 (m, 1H), 3.38-3.19 (m, 4H), 3.04-2.95 (m, 2H), 2.58 (s, 3H), 2.44-2.33 (m, 3H), 2.22-2.17 (m, 1H), 1.95-1.75 (m, 10H), 1.61 (m, 2H), 1.12 (m, 3H). ES-LCMS m/z 717(M+H).

Example 609

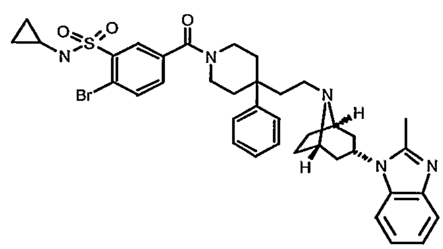
2-bromo-5-[(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenyl piperidin-1-yl)carbonyl]-N-propylbenzenesulfonamide



Method A (HATU). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.14 (s, 1H), 7.80 (d, 1H), 7.68 (d, 1H), 7.48-7.15 (m, 9H), 5.22 (m, 1H), 4.62 (m, 1H), 4.26 (m, 1H), 3.49 (m, 2H), 3.35-3.25 (m, 4H), 2.92-2.85 (m, 2H), 2.58 (s, 3H), 2.44-2.33 (m, 3H), 2.21-2.17 (m, 1H), 1.95-1.75 (m, 10H), 1.61 (m, 2H), 1.52 (m, 2H), 0.89 (m, 3H). ES-LCMS m/z 731(M+H).

Example 610

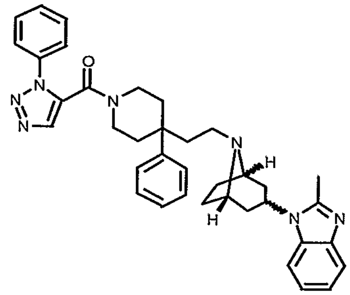
2-bromo-N-cyclopropyl-5-[(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]benzenesulfonamide



Method A (HATU). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.19 (s, 1H), 7.79 (d, 1H), 7.68 (d, 1H), 7.51-7.16 (m, 9H), 5.68 (m, 1H), 4.66 (m, 1H), 4.20 (m, 1H), 4.26 (m, 1H), 3.54-3.27 (m, 5H), 2.58 (s, 3H), 2.41-2.36 (m, 3H), 2.17 (m, 2H), 1.95-1.75 (m, 10H), 1.64 (m, 2H), 0.68 (m, 4H). ES-LCMS m/z 729(M+H).

Example 611

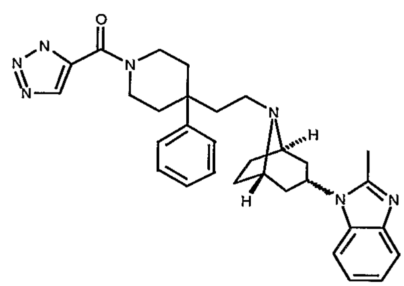
2-methyl-1-[(1R,5S)-8-(2-{4-phenyl-1-[(1-phenyl-1H-1,2,3-triazol-5-yl)carbonyl]piperidin-4-yl}ethyl)-8-azabicyclo[3.2.1]oct-3-yl]-1H-benzimidazole



Method A (HATU). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.84 (s, 1H), 7.70-7.48 (m, 5H), 7.43-7.11 (m, 8H), 4.58 (m, 1H), 4.20-4.10 (m, 1H), 3.22 (m, 4H), 3.01 (m, 1H), 2.40-2.23 (m, 3H), 1.96-1.60 (m, 15H), 1.26 (m, 2H). ES-LCMS m/z 599(M+H).

Example 612

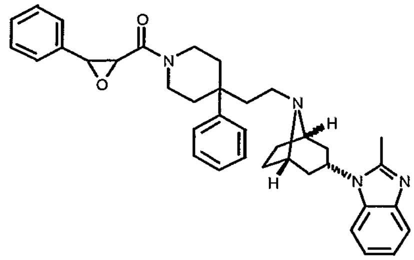
2-methyl-1-((1R,5S)-8-{2-[4-phenyl-1-(1H-1,2,3-triazol-5-ylcarbonyl)piperidin-4-yl]ethyl}-8-azabicyclo[3.2.1] oct-3-yl)-1H-benzimidazole



Method A (HATU). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.13 (s, 1H), 7.70 (d, 1H), 7.40-7.15 (m, 8H), 4.67 (m, 1H), 4.40 (m, 1H), 4.19 (m, 1H), 3.72 (m, 1H), 3.44-3.26 (m, 1H), 2.49-2.21 (m, 8H), 2.01-1.85 (m, 10H), 1.66 (m, 2H), 1.26 (s, 1H). ES-LCMS m/z 523(M+H).

Example 613

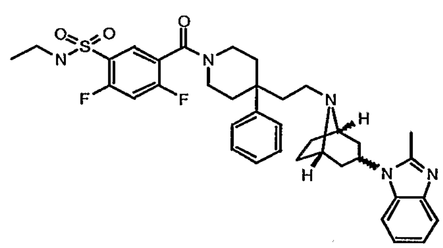
2-methyl-1-[(1R,5S)-8-(2-{4-phenyl-1-[(3-phenyloxiran-2-yl)carbonyl]piperidin-4-yl}ethyl)-8-azabicyclo[3.2.1]oct-3-yl]-1H-benzimidazole



Method A (HATU). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.66 (m, 1H), 7.38-7.16 (m, 13H), 4.59 (m, 1H), 4.08 (m, 1H), 3.62 (m, 1H), 3.24 (m, 2H), 2.59 (s, 3H), 2.55 (m, 1H), 2.34 (m, 2H), 1.93-1.82 (m, 5H), 1.70-1.52 (m, 10H), 1.25 (s, 2H). ES-LCMS m/z 574(M+H).

Example 614

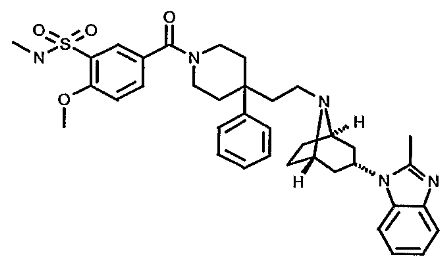
N-ethyl-2,4-difluoro-5-[(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]benzenesulfonamide



Method A (HATU). ^{1}H NMR (300 MHz, methanol-d_4) δ 7.60-7.37 (m, 7H), 7.22 (m, 3H), 6.59 (d, 1H), 4.79 (m, 1H), 3.63 (m, 1H), 3.44 (m, 2H), 3.24 (m, 2H), 2.96 (m, 2H), 2.55 (s, 3H), 2.50-2.33 (m, 2H), 2.12-1.90 (m, 10H), 1.79 (m, 2H), 1.20 (m, 3H), 1.07 (m, 3H). ES-LCMS m/z 675(M+H).

Example 615

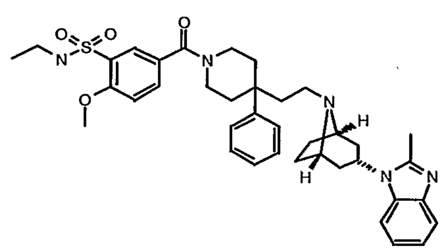
2-methoxy-N-methyl-5-[(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]benzenesulfonamide



Method A (HATU). ^{1}H NMR (300 MHz, methanol-d_4) δ 7.90 (d, 1H), 7.69 (d, 1H), 7.56 (d, 1H), 7.48-7.37 (m, 5H), 7.32-7.19 (m, 4H), 4.78 (m, 1H), 4.03 (s, 3H), 3.39-3.31 (m, 4H), 2.55 (d, 6H), 2.45 (m, 2H), 2.29 (m, 2H), 2.11-1.82 (m, 10H), 1.73 (m, 2H), 1.30 (s, 3H). ES-LCMS m/z 655(M+H).

Example 616

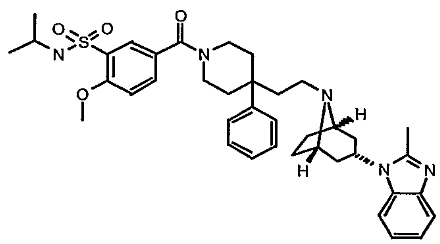
N-ethyl-2-methoxy-5-[(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]benzenesulfonamide



Method A (HATU). ^{1}H NMR (300 MHz, methanol-d_4) δ 7.91 (s, 1H), 7.68 (m, 1H), 7.52 (m, 1H), 7.48-7.36 (m, 5H), 7.32-7.19 (m, 4H), 4.76 (m, 1H), 4.03 (s, 3H), 3.39-3.31 (m, 4H), 2.94 (m, 2H), 2.55 (s, 3H), 2.48-2.39 (m, 4H), 2.09-1.88 (m, 10H), 1.71 (m, 2H), 1.30 (s, 3H), 1.05 (m, 3H). ES-LCMS m/z 669(M+H).

Example 617

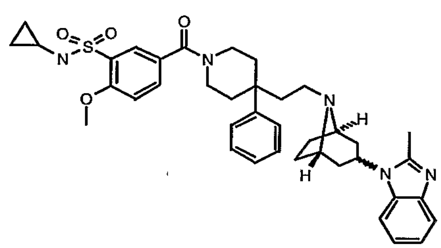
N-isopropyl-2-methoxy-5-[(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]benzenesulfonamide



Method A (HATU). ^{1}H NMR (300 MHz, methanol-d_4) δ 7.92 (d, 1H), 7.70 (m, 1H), 7.52 (m, 1H), 7.43-7.36 (m, 5H), 7.32-7.13 (m, 4H), 4.75 (m, 1H), 4.12 (m, 1H), 4.03 (s, 3H), 3.66 (m, 1H), 3.40-3.31 (m, 6H), 2.54 (s, 3H), 2.48-2.36 (m, 4H), 2.04-1.90 (m, 10H), 1.70 (m, 2H), 1.06 (d, 6H). ES-LCMS m/z 683(M+H).

Example 618

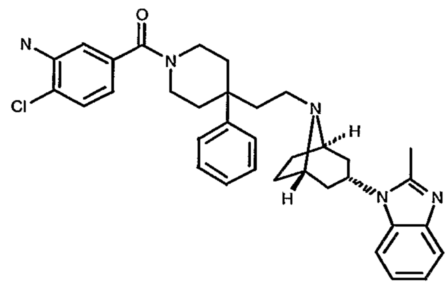
N-cyclopropyl-2-methoxy-5-[(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl] ethyl}-4-phenylpiperidin-1-yl)carbonyl]benzene sulfonamide



Method A (HATU). ^{1}H NMR (300 MHz, methanol-d_4) δ 7.95 (m, 1H), 7.73 (m, 1H), 7.52 (m, 1H), 7.48-7.39 (m, 5H), 7.30-7.15 (m, 4H), 4.76 (m, 1H), 4.17 (m, 1H), 4.03 (s, 3H), 3.69 (m, 1H), 3.40-3.31 (m, 6H), 2.54 (s, 3H), 2.48-2.36 (m, 4H), 2.21-1.90 (m, 10H), 1.71 (m, 2H), 0.55 (m, 4H). ES-LCMS m/z 681(M+H).

Example 619

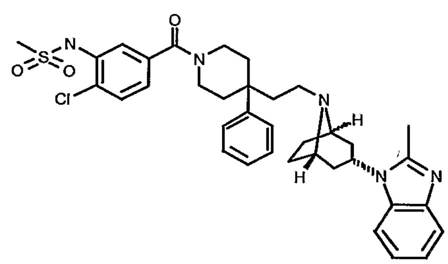
2-chloro-5-[(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]aniline



Method A (HATU). ^{1}H NMR (300 MHz, methanol-d_4) δ 7.53 (m, 1H), 7.41 (m, 5H), 7.27-7.17 (m, 4H), 6.82 (s, 1H), 6.62 (d, 1H), 4.74 (m, 1H), 4.70 (m, 1H), 3.66 (m, 1H), 3.36-3.24 (m, 6H), 2.52 (s, 3H), 2.45-2.40 (m, 2H), 2.22 (m, 1H), 2.02-1.83 (m, 10H), 1.70 (m, 2H). ES-LCMS m/z 581(M+H).

Example 620

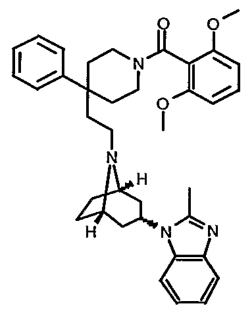
N-{2-chloro-5-[(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]phenyl}methane sulfonamide



Method A (HATU). Intermediate 4-chloro-3-[(methylsulfonyl)amino]benzoic acid was synthesized in same fashion as described in example 639 from precursor example 619. ^{1}H NMR (300 MHz, methanol-d_4) δ 7.72-7.68 (m, 2H), 7.53 (m, 2H), 7.41 (m, 5H), 7.27-7.17 (m, 3H), 4.73 (m, 1H), 4.14 (m, 1H), 3.53 (m, 7H), 3.30 (m, 2H), 2.51 (s, 3H), 2.45-2.29 (m, 4H), 2.01-1.89 (m, 10H), 1.69 (m, 2H). ES-LCMS m/z 659(M+H).

Example 621

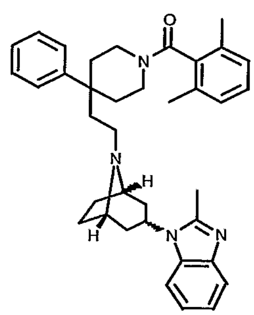
1-((1R,5S)-8-{2-[1-(2,6-dimethoxybenzoyl)-4-phenylpiperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1H-benzimidazole



Acylation via EDCI-HOBt Method P using 2,6-dimethoxybenzoic acid (Aldrich) on 0.21 mmol scale yielded 50 mg (40%) product. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.68 (d, 1H), 7.42-7.15 (m, 9H), 6.68-6.47 (m, 2H), 4.67 (m, 1H), 4.23 (m, 1H), 3.85 (s, 3H), 3.72 (s, 3H), 3.47-3.35 (m, 4H), 3.15-3.04 (m, 1H), 2.55 (s, 3H), 2.48-2.25 (m, 3H), 2.20-2.07 (m, 1H), 2.03-1.72 (m, 10H), 1.65 (m, 2H). HRMS $C_{37}H_{44}N_4O_3$ m/z 593.3492 $(M+H)_{Cal.}$, 593.3478 $(M+H)_{Obs}$.

Example 622

1-((1R,5S)-8-{2-[1-(2,6-dimethylbenzoyl)-4-phenylpiperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1H-benzimidazole

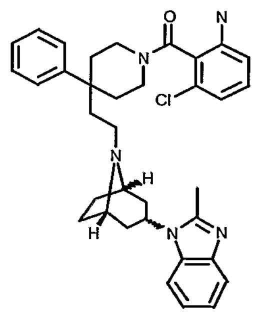


Acylation via EDCI-HOBt Method P using 2,6-dimethylbenzoic acid (Aldrich) on 0.14 mmol scale yielded 53 mg (67%) product. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.87 (m, 1H), 7.51-6.97 (m, 11H), 5.51 (m, 2H), 4.22 (m, 1H), 4.05-3.88 (m, 2H), 3.50 (m, 1H), 3.28 (m, 1H), 3.09 (m, 3H), 2.82 (s, 3H), 2.62

(m, 1H), 2.30 (s, 6H), 2.20-2.02 (m, 10H), 1.88 (m, 1H), 1.71 (m, 1H). HRMS $C_{37}H_{44}N_4O$ m/z 561.3593 $(M+H)_{Cal.}$, 561.3585 $(M+H)_{Obs}$.

Example 623

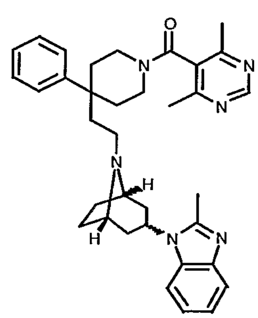
3-chloro-2-[(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]aniline



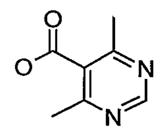
Acylation via EDCI-HOBt Method P using 2-amino-6-chlorobenzoic acid (Aldrich) on 0.14 mmol scale yielded 41 mg (50%) product. ^1H NMR (300 MHz, $CDCl_3$) δ 7.92 (m, 1H), 7.58-7.25 (m, 8H), 7.07 (m, 1H), 6.80-6.55 (m, 2H), 5.50 (m, 1H), 4.26 (m, 5H), 3.99 (m, 3H), 3.50-3.29 (m, 2H), 3.25-3.09 (m, 1H), 2.99 (m, 2H), 2.83 (s, 3H), 2.20-2.58 (m, 2H), 2.42-2.02 (m, 9H). HRMS $C_{35}H_{40}ClN_5O$ m/z 582.3000 $(M+H)_{Cal.}$, 582.3002 $(M+H)_{Obs}$.

Example 624

1-[(1R,5S)-8-(2-{1-[(4,6-dimethylpyrimidin-5-yl)carbonyl]-4-phenylpiperidin-4-yl}ethyl)-8-azabicyclo[3.2.1]oct-3-yl]-2-methyl-1H-benzimidazole



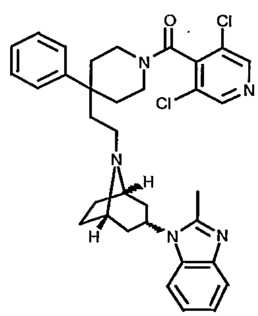
4,6-Dimethylpyrimidine-5-carboxylic acid was synthesized according to the procedure outlined in WO 00/66558, Schering Corporation, 2000, pages 67-69. Overall yield was 12% (3 steps).



Acylation via EDCI-HOBt Method P using 4,6-dimethylpyrimidine-5-carboxylic acid on 0.16 mmol scale yielded 46 mg (51%) of the product. ^1H NMR (300 MHz, $CDCl_3$) δ 8.92 (s, 1H), 7.55 (m, 1H), 7.43 (m, 5H), 7.20 (m, 3H), 4.88 (s, 1H), 4.74 (m, 1H), 4.27 (m, 1H), 3.51-3.07 (m, 5H), 2.54 (s, 6H), 2.50-2.20 (m, 7H), 2.05-1.84 (m, 9H), 1.69 (m, 2H). HRMS $C_{35}H_{42}N_6O$ m/z 563.3498 $(M+H)_{Cal.}$, 563.3483 $(M+H)_{Obs}$.

Example 625

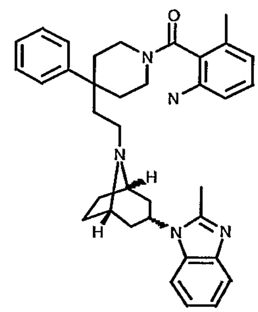
N-((1R,5S)-8-{2-[1-(3,5-dichloroisonicotinoyl)-4-phenylpiperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-N-[(2Z,4Z)-hexa-2,4-dienyl]ethanimidamide



Acylation via EDCI-HOBt Method P using 4,6-dichloroisonicotinic acid (TCI America) on 0.16 mmol scale yielded 53 mg (55%) of the product. ^1H NMR (300 MHz, $CDCl_3$) δ 8.66 (s, 1H), 8.61 (s, 1H), 7.54 (d, 1H), 7.42 (m, 5H), 7.30-7.1 (m, 3H), 4.75 (m, 1H), 4.26 (m, 1H), 3.48-3.30 (m, 5H), 3.19 (m, 1H), 2.54 (s, 3H), 2.45-2.26 (m, 4H), 2.10-1.84 (m, 10H), 1.71(m, 2H). HRMS $C_{34}H_{37}Cl_2N_5O$ m/z 602.2453 $(M+H)_{Cal}$, 602.2476 $(M+H)_{Obs}$.

Example 626

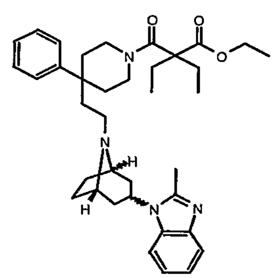
3-methyl-2-[(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]aniline



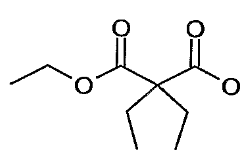
Acylation via EDCI-HOBt Method P using 2-amino-6-methylbrnzoic acid (Aldrich) on 0.1 6mmol scale yielded 39 mg (43%) of the product. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55 (m, 1H), 7.42 (m, 5H), 7.20 (m, 3H), 7.03 (m, 1H), 6.70-6.53 (m, 2H), 4.88 (s, 3H), 4.74 (m, 1H), 4.20 (m, 1H), 3.55-3.26 (m, 3H), 2.27 (m, 2H), 2.10-1.84 (m, 10H), 1.71 (m, 2H), 1.30 (s, 1H). HRMS $C_{36}H_{43}N_5O$ m/z 562.3546 $(M+H)_{Cal}$, 562.3544 $(M+H)_{Obs}$.

Example 627

ethyl 2-ethyl-2-[(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperdin-1-yl)carbonyl]butonate



Preparation of 2-(ethoxycarbonyl)-2-ethylbutanoic acid



A solution of diethyl-malonic acid diethyl ester (3.0 g, 13.89 mmol) and potassium hydroxide (0.778 g, 13.89 mmol) in ethanol (50 ml) was stirred at

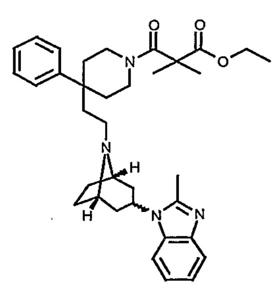
room temperature for 18 hrs. The solvent was evaporated off and the residue was dissolved in water (20 ml) and extracted with dichloromethane (20 ml). This organic layer was discarded. The aqueous layer was then acidified with concentrated HCl and extracted with dichloromethane (3 x 20 ml). The combined organic layers were dried over magnesium sulfate and concentrated to give a colorless oil (1.9 g, 72%). ^{1}H NMR (300 MHz, methanol-d_4) δ 4.17 (m, 2H), 1.89 (m, 4H), 1.25 (m, 3H), 0.83 (m, 6H). ES-LCMS m/z 188 (M+H).

Preparation of ethyl 2-ethyl-2-[(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperdin-1-yl)carbonyl]butonate (example 627)

Acylation via EDCI-HOBt Method P using 2-(ethoxycarbonyl)-2-ethylbutanoic acid on 0.21mmol scale yielded 115 mg (91%) of colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.88 (d, 1H), 7.67 (m, 2H), 7.40-7.18 (m, 6H), 4.87 (m, 1H), 4.75-4.40 (m, 2H), 4.22 (m, 3H), 3.41 (m, 2H), 3.12 (m, 2H), 2.55 (s, 3H), 2.45 (m, 1H), 2.20-1.61 (m, 16H), 1.44 (s, 1H), 1.21 (m, 3H), 0.92-0.70 (m, 6H). HRMS $C_{37}H_{50}N_4O_3$ m/z 599.3961 $(M+H)_{Cal}$, 599.3981 $(M+H)_{Obs}$.

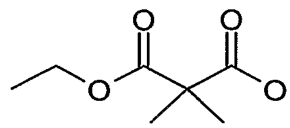
<u>Example 628</u>

<u>ethyl 2,2-dimethyl-3-(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)-3-oxopropanoate</u>



3-Ethoxy-2,2-dimethyl-3-oxopropanoic acid was prepared as in the case of diethyl dimethylmalonate on 15.96 mmol scale to give product as a

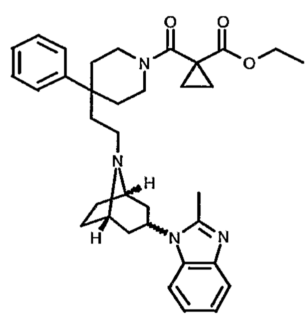
colorless oil (1.8 g, 70%). [1]H NMR (300 MHz, methanol-d_4) δ 4.17 (m, 2H), 1.43 (s, 6H), 1.25 (m, 3H). ES-LCMS m/z 160 (M+H).



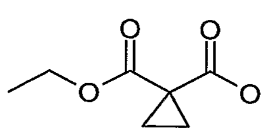
The ompound in example 628 was prepared via acylation (EDCI-HOBt Method P) using 3-ethoxy-2,2-dimethyl-3-oxopropanoic acid on 0.21 mmol scale, yielding 98 mg (82%) of the product as a colorless oil. [1]H NMR (300 MHz, $CDCl_3$) δ 7.69 (d, 1H), 7.38 (m, 2H), 7.28 (m, 4H), 7.17 (m, 2H), 4.69 (m, 1H), 4.17 (m, 2H), 3.30 (m, 2H), 3.08 (m, 1H), 2.58 (s, 3H), 2.39 (m, 2H), 2.20 (m, 2H), 1.97-1.60 (m, 12H), 1.50-1.37 (m, 4H), 1.30-1.18 (m, 5H), 0.87 (m, 2H). HRMS $C_{35}H_{46}N_4O_3$ m/z 571.3648 $(M+H)_{Cal}$, 571.3646 $(M+H)_{Obs}$.

Example 629

ethyl 1-[(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]cyclopropanecarboxylate



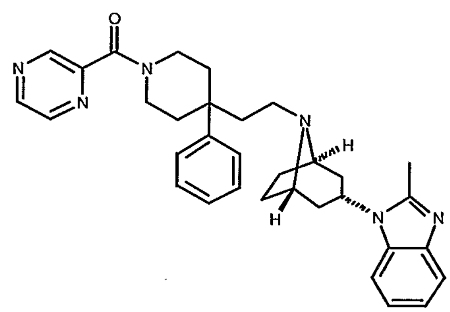
1-(Ethoxycarbonyl)cyclopropanecarboxylic acid was prepared as described in in case of diethyl 1,1-cyclopropanedicarboxylate on 16.13 mmol scale to give product as a colorless oil (2.1 g, 82%). [1]H NMR (300 MHz, methanol-d_4) δ 3.95 (m, 2H), 1.43 (s, 4H), 0.98 (m, 3H). ES-LCMS m/z 158 (M+H).



The compound in example 629 was prepared by acylation via EDCI-HOBt Method P using 1-(ethoxy carbonyl)cyclopropanecarboxylic acid on 0.21 mmol scale, yielding 82 mg (68%) product as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.67 (m, 1H), 7.45-7.10 (m, 8H), 4.62 (m, 1H), 4.15 (m, 2H), 3.69 (m, 1H), 3.26 (m, 4H), 2.58 (s, 3H), 2.44-2.15 (m, 5H), 1.97-1.76 (m, 10H), 1.63 (m, 2H), 1.45 (m, 3H), 1.35-1.16 (m, 5H). HRMS $C_{35}H_{44}N_4O_3$ m/z 569.3492 $(M+H)_{Cal}$, 569.3503 $(M+H)_{Obs}$.

Example 630

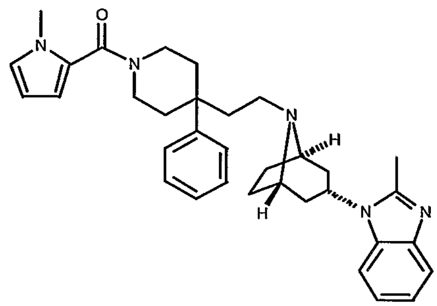
2-methyl-1-((1R,5S)-8-{2-[4-phenyl-1-(pyrazin-2-ylcarbonyl)piperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-1H-benzimidazole



The title compound was obtained by method A (HATU) using 2-pyrizinecarboxylic acid on 0.16 mmol scale. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.89 (s, 1H), 8.59 (dd, 2H), 7.67 (m, 1H), 7.45-7.10 (m, 8H), 4.61 (m, 1H), 4.32-4.05 (m, 1H), 3.71 (m, 1H), 3.44-3.21 (m, 4H), 2.56 (s, 3H), 2.42-2.22 (m, 4H), 2.00-1.79 (m, 10H), 1.63 (m, 2H). ES-LCMS m/z 534(M+H).

Example 631

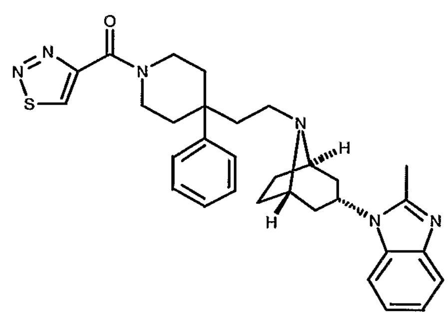
2-methyl-1-[(1R,5S)-8-(2-{1-[(1-methyl-1H-pyrrol-2-yl)carbonyl]-4-phenylpiperidin-4-yl}ethyl)-8-azabicyclo[3.2.1]oct-3-yl]-1H-benzimidazole



The title compound in example 631 was synthesized using method A (HATU) with 1-methyl-1*H*-pyrrole-2-carboxylic acid on 0.16 mmol scale. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.65 (d, 1H), 7.45-7.12 (m, 8H), 6.68 (s, 1H), 6.30 (d, 1H), 6.08 (m, 1H), 4.62 (m, 1H), 4.04 (m, 2H), 3.76 (s, 3H), 3.44 (m, 2H), 3.26 (m, 2H), 2.57 (s, 3H), 2.44-2.18 (m, 4H), 2.03-1.78 (m, 10H), 1.63 (m, 2H). ES-LCMS m/z 535(M+H).

Example 632

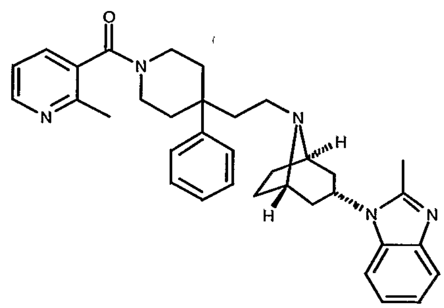
2-methyl-1-((1R,5S)-8-{2-[4-phenyl-1-(1,2,3-thiadiazol-4-ylcarbonyl)piperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-1H-benzimidazole



The title compound in example 632 was synthesized using method A (HATU) utilizing 1,2,3-thiadiazole-4-carboxylic acid on 0.16 mmol scale. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.97 (m, 1H), 7.72-7.51 (m, 1H), 7.45-7.00 (m, 8H), 5.25 (m, 2H), 4.55 (m, 1H), 4.21 (m, 2H), 3.68-3.09 (m, 4H), 2.60-2.20 (m, 5H), 2.02-1.72 (m, 10H), 1.53 (m, 2H). ES-LCMS m/z 540(M+H).

Example 633

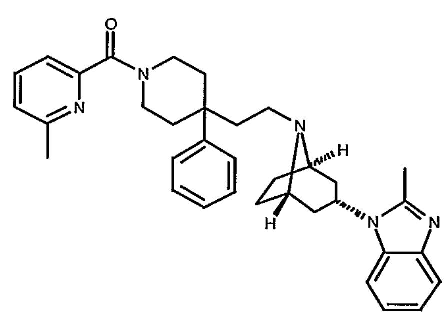
2-methyl-1-[(1R,5S)-8-(2-{1-[(2-methylpyridin-3-yl)carbonyl]-4-phenylpiperidin-4-yl}ethyl)-8-azabicyclo[3.2.1]oct-3-yl]-1H-benzimidazole



The title compound in example 633 was synthesized using method A (HATU) utilizing 2-methylnicotinic acid on 0.16 mmol scale. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.54 (d, 1H), 7.65 (m, 1H), 7.45-7.08 (m, 10H), 4.61 (m, 1H), 4.28 (m, 1H), 3.45-3.07 (m, 5H), 2.65-2.48 (m, 4H), 2.43-2.30 (m, 5H), 2.22-2.03 (m, 2H), 1.97-1.77 (m, 8H), 1.63 (m, 2H). ES-LCMS m/z 547(M+H).

Example 634

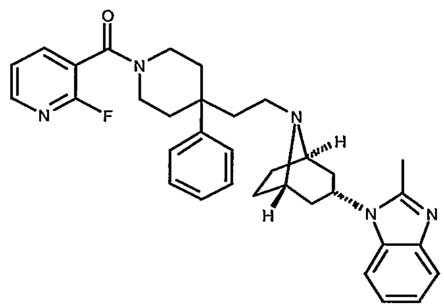
2-methyl-1-[(1R,5S)-8-(2-{1-[(6-methylpyridin-2-yl)carbonyl]-4-phenylpiperidin-4-yl}ethyl)-8-azabicyclo[3.2.1]oct-3-yl]-1H-benzimidazole



The title compound in example 634 was synthesized using method A (HATU) utilizing 6-methylpyridine-2-carboxylic acid on 0.16 mmol scale. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.66 (m, 2H), 7.45-7.09 (m, 10H), 4.62 (m, 1H), 4.22 (m, 1H), 3.65 (m, 1H), 3.50-3.20 (m, 4H), 2.56 (m, 6H), 2.36 (m, 3H), 2.17 (m, 1H), 2.0-1.80 (m, 10H), 1.63 (m, 2H). ES-LCMS m/z 547(M+H).

Example 635

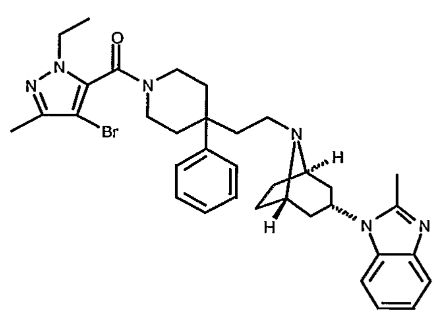
1-[(1R,5S)-8-(2-{1-[(2-fluoropyridin-3-yl)carbonyl]-4-phenylpiperidin-4-yl}ethyl)-8-azabicyclo[3.2.1]oct-3-yl]-2-methyl-1H-benzimidazole



The title compound in example 635 was synthesized using method A (HATU) utilizing 2-fluoronicotinic acid on 0.16 mmol scale. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.28 (d, 1H), 7.84 (m, 1H), 7.68 (m, 1H), 7.45-7.20 (m, 9H), 4.61 (m, 1H), 4.27 (m, 1H), 3.45-3.15 (m, 5H), 2.56 (s, 3H), 2.35 (m, 3H), 2.20 (m, 1H), 1.98-1.73 (m, 10H), 1.67-1.5 5(m, 2H). ES-LCMS m/z 551(M+H).

Example 636

1-[(1R,5S)-8-(2-{1-[(4-bromo-1-ethyl-3-methyl-1H-pyrazol-5-yl)carbonyl]-4-phenylpiperidin-4-yl}ethyl)-8-azabicyclo[3.2.1]oct-3-yl]-2-methyl-1H-benzimidazole

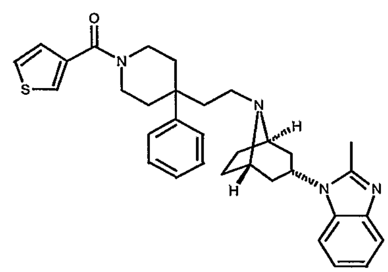


The title compound in example 636 was synthesized using method A (HATU) utilizing 4-bromo-1-ethyl-3-methyl-1*H*-pyrazole-5-carboxylic acid on 0.16 mmol scale. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.66 (d, 1H), 7.50-7.05 (m, 8H), 4.64 (m, 1H), 4.30-2.86 (m, 2H), 3.55 (m, 1H), 3.40-3.28 (m, 4H), 2.58 (s,

3H), 2.37 (m, 3H), 2.25 (m, 3H), 2.12-1.78 (m, 10H), 1.65 (m, 2H), 1.46 (m, 2H), 1.33 (m, 3H). ES-LCMS m/z 642(M+H).

Example 637

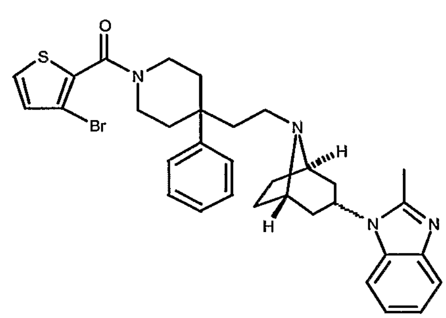
2-methyl-1-((1R,5S)-8-{2-[4-phenyl-1-(thien-3-ylcarbonyl)piperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-1H-benzimidazole



The title compound in example 637 was synthesized using method A (HATU) utilizing thiophene-3-carboxylic acid on 0.16 mmol scale. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.66 (d, 1H), 7.54-7.20 (m, 11H), 4.62 (m, 1H), 4.15 (m, 1H), 3.74 (m, 1H), 3.42-3.20 (m, 4H), 2.57 (s, 3H), 2.45-2.12 (m, 4H), 2.05-1.25 (m, 10H), 1.64 (m, 2H). ES-LCMS m/z 538(M+H).

Example 638

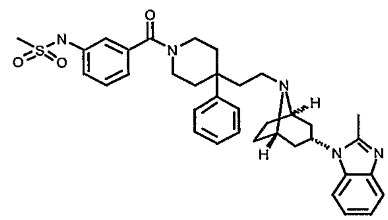
1-[(1R,5S)-8-(2-{1-[(3-bromothien-2-yl)carbonyl]-4-phenylpiperidin-4-yl}ethyl)-8-azabicyclo[3.2.1]oct-3-yl]-2-methyl-1H-benzimidazole



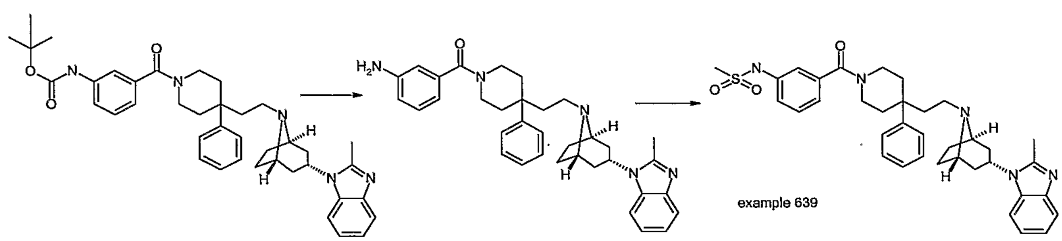
The title compound in example 638 was synthesized using method A (HATU) utilizing 3-bromothiophene-2-carboxylic acid on 0.16 mmol scale. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.68 (d, 1H), 7.45-7.10 (m, 9H), 6.97 (d, 1H), 4.63

(m, 1H), 4.15 (m, 1H), 3.63 (m, 1H), 3.37-3.28 (m, 4H), 2.57 (s, 3H), 2.48-2.22 (m, 4H), 2.05-1.80 (m, 10H), 1.65 (m, 2H). ES-LCMS m/z 616(M+H).

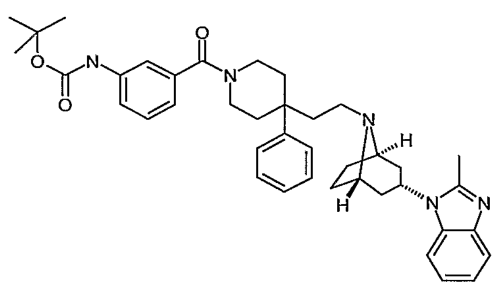
Example 639



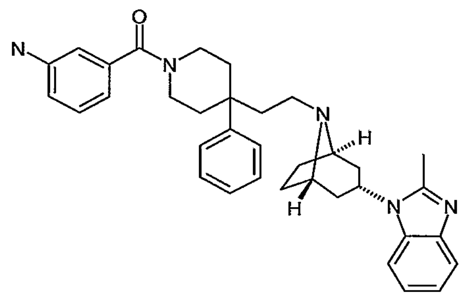
N-{3-[(4-{2-[(1R,5S)-3-(2-Methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]phenyl}methane sulfonamide was synthesized as in the following scheme.



tert-butyl 3-[(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]phenylcarbamate was prepared by Method A (HATU) using 3-[(*tert*-butoxycarbonyl)amino]benzoic acid on 1.64 mmol scale. Purification by reverse phase chromatography on C18 using Acetonitrile:water 10:90 to 90:10 and removal of solvent gave 635 mg of product (60%). ES-LCMS m/z 647(M+H).



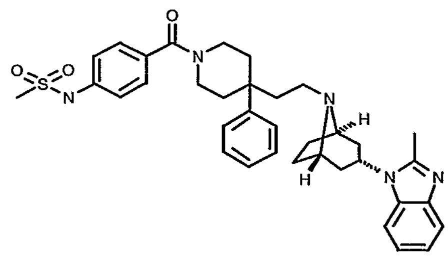
3-[(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]phenylamine was obtained by dissolving of Boc-derivative coupling product in 20 ml dichloromethane and treatment with 2 ml of trifluoroacetic acid at room temperature for 2 hrs. Removal of solvent gave product in quantative yield. ES-LCMS m/z 547(M+H).



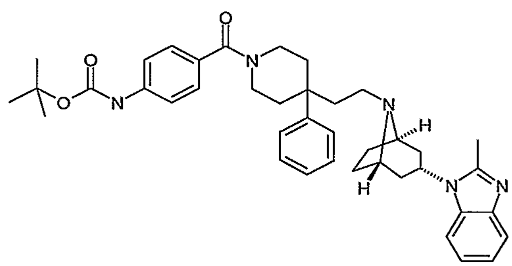
N-{3-[(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]phenyl}methane sulfonamide was synthesized by dissolving the amine precursor (60 mg, 0.11 mmol) in 3 ml dichloromethane cooled to 0°C, followed by addition of 2 eq of Hunig base and methane sulfonyl chloride (12 mg, 0.11 mmol) and stirring overnight at room temperature. The solution was then diluted with DCM and washed with Na_2CO_3, dried organic layer with $MgSO_4$ and rotovapped to dryness. Purified by reverse phase chromatography on C18 using Acetonitrile:water 10:90 to 90:10. Removal of solvent gave 38 mg (56%) of the product. ^1H NMR (300 MHz, methanol-d_4) δ 7.83 (m, 2H), 7.68-7.43 (m, 9H), 7.33 (m, 1H), 5.34 (m, 1H), 4.21-4.11 (m, 3H), 3.63 (m, 1H), 3.46 (s, 3H), 3.38-3.27 (m, 4H), 2.97 (m, 2H), 2.85 (s, 3H), 2.79 (m, 2H), 2.46 (m, 3H), 2.29-2.19(m, 7H), 1.99-1.87 (m, 2H). ES-LCMS m/z 625(M+H).

Example 640

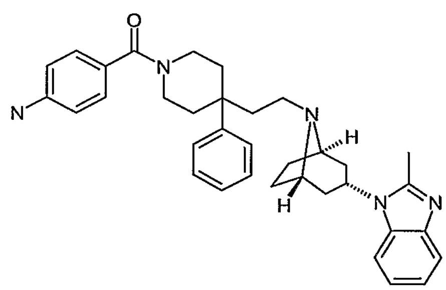
N-{4-[(4-{2-[(1R,5S)-3-(2-Methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]phenyl}methane sulfonamide was synthesized similarly to the title compound in example 639.



Tert-butyl 4-[(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]phenylcarbamate was prepared as described in example 639 using 4-[(tert-butoxycarbonyl)amino]benzoic acid to give 545 mg (53%) of product. ES-LCMS m/z 647(M+H).



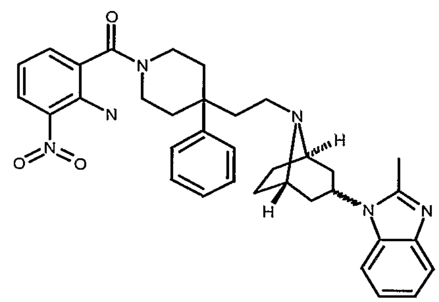
4-[(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]phenylamine was prepared as in example 639. ES-LCMS m/z 547(M+H).



The title compound in example 640 (N-{4-[(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]phenyl}methanesulfonamide) was prepared as described for example 639 to give 28 mg (40%) of the title product of example 640. ^{1}H NMR (300 MHz, methanol-d_4) δ 7.85 (m, 2H), 7.66-7.41 (m, 10H), 7.33 (m, 1H), 5.39 (m, 1H), 4.21-4.09 (m, 3H), 3.63 (m, 1H), 3.46 (s, 6H), 2.97-2.92 (m,

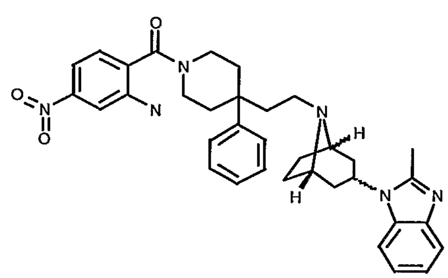
2H), 2.85 (s, 3H), 2.73(m, 2H), 2.46-2.37 (m, 3H), 2.24 (m, 7H), 1.97-1.90 (m, 2H). ES-LCMS m/z 625(M+H).

Example 641



2-[(4-{2-[(1R,5S)-3-(2-Methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]-6-nitrophenylamine was synthesized by method B (Anhydride) using 4-nitroisatoic anhydride on 0.16 mmol scale. ^{1}H NMR (300 MHz, methanol-d_4) δ 7.80 (m, 1H), 7.60 (m, 3H), 7.46 (m, 5H), 7.31-7.25 (m, 2H), 5.31 (m, 1H), 4.20-4.10 (m, 2H), 3.52 (m, 1H), 3.35-3.22 (m, 3H), 2.94 (m, 2H), 2.82 (s, 3H), 2.75 (m, 2H), 2.40 (m, 3H), 2.20 (m, 7H), 1.93-1.86 (m, 2H). ES-LCMS m/z 592(M+H).

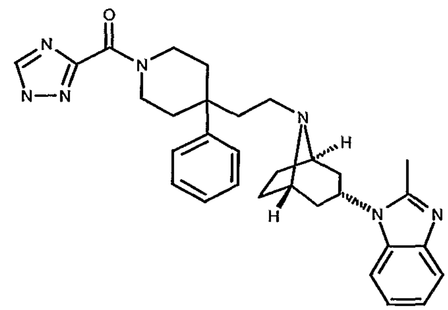
Example 642



2-[(4-{2-[(1R,5S)-3-(2-Methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]-5-nitrophenylamine was synthesized by method B (Anhydride) using 5-nitroisatoic anhydride on 0.16 mmol scale. ^{1}H NMR (300 MHz, methanol-d_4) δ 8.00 (d, 2H), 7.78 (m, 2H), 7.60 (m, 2H), 7.45 (m, 4H), 7.31 (m, 1H) 6.79 (d,

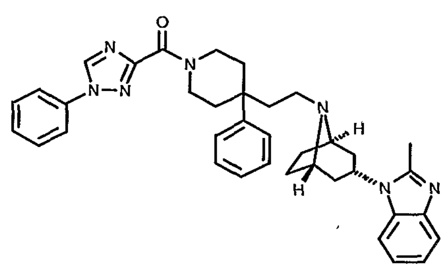
1H), 5.30 (m, 1H), 4.10 (m, 2H), 3.40-3.22 (m, 4H), 2.94 (m, 2H), 2.81 (m, 3H), 2.75 (m, 2H), 2.45-2.14 (m, 10H), 1.92-1.90 (m, 2H). ES-LCMS m/z 592(M+H).

Example 643



2-Methyl-1-((1R,5S)-8-{2-[4-phenyl-1-(1H-1,2,4-triazol-3-ylcarbonyl)piperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-1H-benzimidazole was synthesized by method A (HATU) using 1*H*-1,2,4-triazole-3-carboxylic acid on 0.16 mmol scale. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.09 (s, 1H), 7.68 (m, 1H), 7.45-7.11 (m, 8H), 4.93 (m, 1H), 4.64 (m, 1H), 4.21 (m, 1H), 3.83 (m, 1H), 3.37-3.25 (m, 2H), 2.37 (m, 3H), 2.05-1.81 (m, 7H), 1.78-1.55 (m, 11H). ES-LCMS m/z 523(M+H).

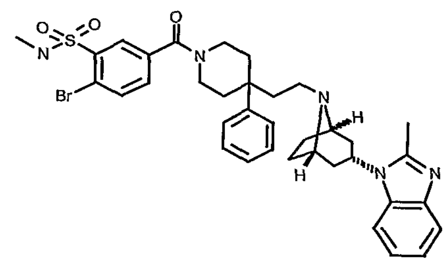
Example 644



2-Methyl-1-[(1R,5S)-8-(2-{4-phenyl-1-[(1-phenyl-1H-1,2,4-triazol-3-yl)carbonyl]piperidin-4-yl}ethyl)-8-azabicyclo[3.2.1]oct-3-yl]-1H-benzimidazole was synthesized by method A (HATU) using 1-phenyl-1*H*-1,2,4-triazole-3-carboxylic acid on 0.16 mmol scale. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.75-7.61 (m, 2H), 7.57-7.10 (m, 12H), 4.63 (m, 1H), 4.31 (m, 1H), 4.06 (m, 1H), 3.55-

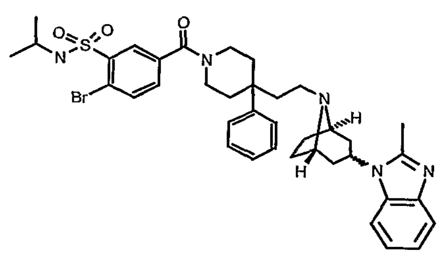
3.38 (m, 2H), 3.25 (m, 2H), 2.37 (m, 4H), 2.04-1.61 (m, 14H), 1.26 (m, 2H). ES-LCMS m/z 599(M+H).

Example 645



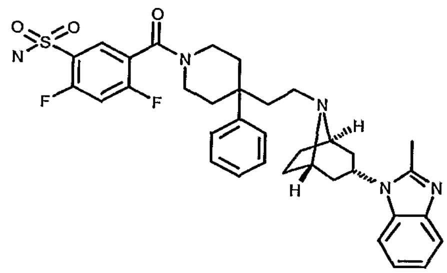
2-Bromo-N-methyl-5-[(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]benzene sulfonamide was obtained by method A (HATU) using acid 38 on 0.09 mmol scale. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.14 (s, 1H), 7.79 (d, 1H), 7.66 (d, 1H), 7.52-7.08 (m, 9H), 5.47 (m, 1H), 4.62 (m, 1H), 4.25 (m, 1H), 3.50 (m, 1H), 3.26 (m, 4H), 2.57 (s, 3H), 2.39 (m, 3H), 2.18 (m, 1H), 2.04-1.58 (m, 12H), 1.27 (s, 3H). ES-LCMS m/z 703(M+H).

Example 646



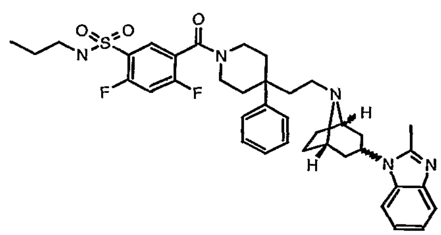
2-Bromo-N-isopropyl-5-[(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]benzene sulfonamide was obtained by method A (HATU) using Acid 41 on 0.09 mmol scale. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.16 (s, 1H), 7.80 (d, 1H), 7.65 (d, 1H), 7.50-7.08 (m, 9H), 5.09 (m, 1H), 4.63 (m, 1H), 4.23 (m, 1H), 3.46 (m, 1H), 3.26 (m, 4H), 2.58 (s, 3H), 2.36 (m, 3H), 2.18 (m, 1H), 2.00-1.75 (m, 10H), 1.65-1.58 (m, 2H), 1.12 (m, 6H). ES-LCMS m/z 731(M+H).

Example 647



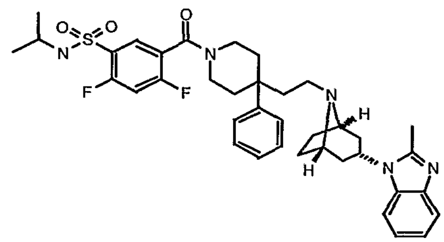
2,4-Difluoro-5-[(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]benzene sulfonamide was obtained by method A (HATU) using Acid 31 on 0.14 mmol scale. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40 (m, 2H), 7.30-7.10 (m, 9H), 4.84 (m, 1H), 4.24 (m, 1H), 3.40 (m, 2H), 2.98 (s, 3H), 2.30 (m, 5H), 2.15-1.72 (m, 12H). ES-LCMS m/z 647(M+H).

Example 648



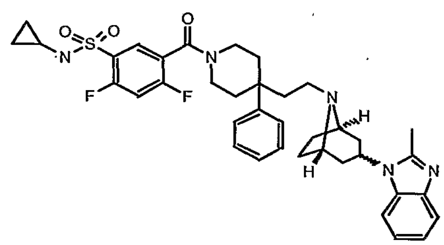
2,4-Difluoro-5-[(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]-N-propylbenzenesulfonamide was obtained by method A (HATU) using Acid 34 on 0.14 mmol scale. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.56 (m, 1H), 7.45-7.15 (m, 10H), 4.74 (m, 1H), 4.23 (m, 1H), 3.50-3.16 (m, 6H), 2.94 (m, 2H), 2.55 (s, 3H), 2.43 (m, 4H), 2.12-1.86 (m, 10H), 1.74 (m, 2H), 1.51 (m, 2H), 0.89 (m, 3H). ES-LCMS m/z 689(M+H).

Example 649



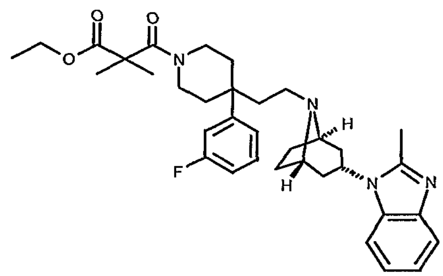
2,4-Difluoro-N-isopropyl-5-[(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl] benzenesulfonamide was obtained by method A (HATU) using Acid 35 on 0.14 mmol scale. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.68 (m, 1H), 7.45-7.15 (m, 9H), 7.00 (m, 1H), 4.83 (m, 1H), 4.62 (m, 1H), 4.28 (m, 1H), 3.60-3.18 (m, 6H), 2.58 (s, 3H), 2.44-2.15 (m, 4H), 2.00-1.76 (m, 10H), 1.62 (m, 2H), 1.13 (m, 6H). ES-LCMS m/z 689(M+H).

Example 650



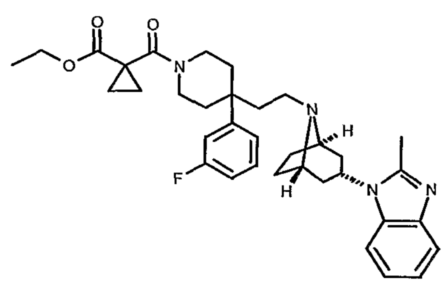
N-Cyclopropyl-2,4-difluoro-5-[(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1] oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]benzene sulfonamide was obtained by Method A (HATU) using Acid 36 on 0.14 mmol scale. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.67 (m, 1H), 7.45-7.22 (m, 8H), 7.10 (m, 2H), 4.61 (m, 1H), 4.24 (m, 1H), 3.36-3.24 (m, 5H), 2.57 (s, 3H), 2.29 (m, 5H), 1.95-1.60 (m, 10H), 1.62 (m, 2H), 1.25 (s, 4H). ES-LCMS m/z 687(M+H).

Example 651



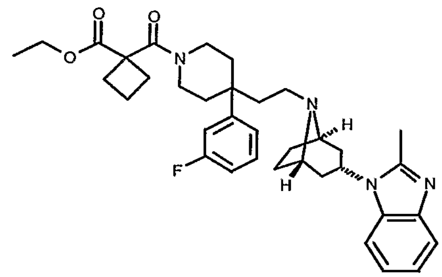
Ethyl 3-(4-(3-fluorophenyl)-4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)-2,2-dimethyl-3-oxopropanoate was obtained by Method A (HATU) using 3-ethoxy-2,2-dimethyl-3-oxopropanoic acid on 0.21 mmol scale. ^{1}H NMR (300 MHz, methanol-d$_4$) δ 7.55 (m, 1H), 7.43 (m, 2H), 7.19 (m, 4H), 7.00 (m, 1H), 4.72 (m, 1H), 4.19 (m, 2H), 3.32 (m, 4H), 2.56 (s, 3H), 2.41 (m, 2H), 2.20 (m, 2H), 2.08-1.79 (m, 10H), 1.69 (m, 2H), 1.40 (s, 5H), 1.25 (m, 6H). ES-LCMS m/z 588(M+H).

Example 652



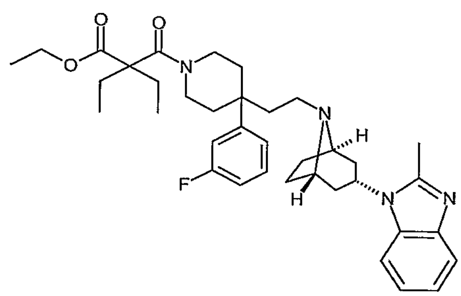
Ethyl 1-[(4-(3-fluorophenyl)-4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)carbonyl]cyclopropane carboxylate was obtained by Method A (HATU) using 1-(ethoxycarbonyl)cyclopropanecarboxylic acid on 0.21 mmol scale. ^{1}H NMR (300 MHz, methanol-d$_4$) δ 7.55 (m, 1H), 7.44 (m, 2H), 7.19 (m, 4H), 7.00 (m, 1H), 4.75 (m, 1H), 4.16 (m, 2H), 4.00 (m, 1H), 3.83 (m, 1H), 3.32 (m, 3H), 2.56 (s, 3H), 2.46 (m, 2H), 2.29 (m, 2H), 2.10-1.83 (m, 10H), 1.69 (m, 2H), 1.47 (s, 2H), 1.27 (m, 6H). ES-LCMS m/z 586(M+H).

Example 653



Ethyl 1-[(4-(3-fluorophenyl)-4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)carbonyl]cyclobutane carboxylate was obtained by Method A (HATU) using 1-(ethoxycarbonyl)cyclobutanecarboxylic acid on 0.21 mmol scale. ^{1}H NMR (300 MHz, methanol-d_4) δ 7.55 (m, 1H), 7.40 (m, 2H), 7.20 (m, 4H), 7.00 (m, 1H), 4.74 (m, 1H), 4.19 (m, 2H), 3.95 (m, 1H), 3.32 (m, 5H), 3.04 (m, 1H), 2.56 (s, 3H), 2.44 (m, 4H), 2.05-1.78 (m, 10H), 1.70 (m, 2H), 1.27 (m, 6H). ES-LCMS m/z 600(M+H).

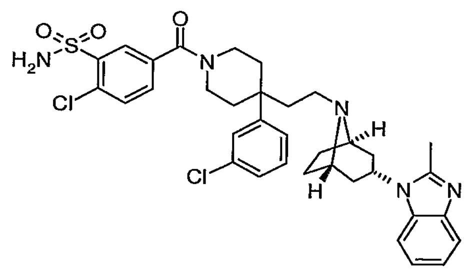
Example 653B



Ethyl 2-ethyl-2-[(4-(3-fluorophenyl)-4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)carbonyl]butanoate was obtained by Method A (HATU) using 2-(ethoxycarbonyl)-2-ethylbutanoic acid on 0.21 mmol scale. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70 (d, 1H), 7.33 (m, 3H), 7.07 (m, 4H), 4.64 (m, 1H), 4.18 (m, 2H), 3.50 (m, 1H), 3.24 (m, 4H), 2.57 (s, 3H), 2.38 (m, 2H), 2.14 (m, 2H), 1.94-1.69 (m, 10H), 1.62 (m, 2H), 1.24 (m, 7H), 0.77 (m, 5H). ES-LCMS m/z 616(M+H).

Example 654

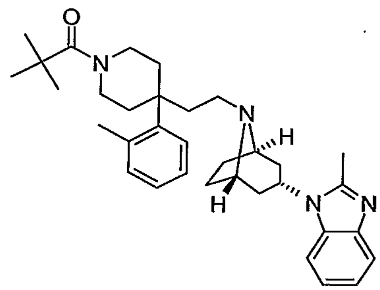
2-Chloro-5-[(4-(3-chlorophenyl)-4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)carbonyl]benzenesulfonamide



A mixture of 1-((1*R*,5*S*)-8-{2-[4-(3-chlorophenyl)piperidin-4-yl]ethyl}-8-azabicyclo[3.2.1] oct-3-yl)-2-methyl-1*H*-benzimidazole dihydrochloride (0.15 g, 0.32 mmol), 4-chloro-3-sulfamoylbenzoic acid (0.076 g, 0.32 mmol) and triethylamine (0.14 mL, 1 mmol) in dimethylformamide (1 mL) was treated with O-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (0.133 g, 0.35 mmol) and the resulting mixture was stirred for 1 h at rt. The mixture was diluted with water and the resulting precipitate was collected, washed with saturated sodium bicarbonate and water, dried and purified by chromatography on silica gel eluting with a 120:15:1 to 60:15:1 gradient of chloroform:methanol:ammonium hydroxide to give 2-chloro-5-[(4-(3-chlorophenyl)-4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)carbonyl]benzenesulfonamide as a white solid (0.052 g, 24%). ^{1}H NMR (400 MHz, CD_3OD_3) δ 8.09 (s, 1H), 7.90 (s, 1H), 7.69 (m, 1H), 7.62 (m, 1H), 7.53 (m, 1H), 7.38–7.46 (m, 3H), 7.27–7.38 (m, 1H), 7.17–7.20 (m, 2H), 4.74 (m, 1H), 4.11 (m, 1H), 3.58 (m, 2H), 3.40 (m, 2H), 3.16–3.22 (m, 1H), 2.54 (s, 3H), 2.41–2.49 (m, 2H), 2.33–2.38 (m, 1H), 2.20–2.26 (m, 1H), 1.94–2.12 (m, 10H), 1.68–1.74 (m, 2H). HRMS $C_{35}H_{39}Cl_2N_5O_3S$ *m/z* 680.2229 $(M+H)_{Cal.}$, 680.2239 $(M+H)_{Obs.}$.

Example 655

1-((1R,5S)-8-{2-[1-(2,2-Dimethylpropanoyl)-4-(2-methylphenyl)piperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1H-benzimidazole



Tert-butyl 4-(1-cyano-2-ethoxy-2-oxoethyl)-4-(2-methylphenyl)piperidine-1-carboxylate. Using the same procedure as in Example 16b 1-bromo-2-methylbenzene (5.1 g, 30 mmol) was used in place of 1-chloro-3-iodobenzene to give *tert*-butyl 4-(1-cyano-2-ethoxy-2-oxoethyl)-4-(2-methylphenyl)piperidine-1-carboxylate as an oil that was used without further purification.

[1-(tert-Butoxycarbonyl)-4-(2-methylphenyl)piperidin-4-yl](cyano)acetic Acid. *tert*-Butyl 4-(1-cyano-2-ethoxy-2-oxoethyl)-4-(2-methylphenyl)piperidine-1-carboxylate was hydrolysed using the same procedure as in Example 16c to give [1-(*tert*-butoxycarbonyl)-4-(2-methylphenyl) piperidin-4-yl](cyano)acetic acid as an amber foam that was used without further purification.

tert-Butyl 4-(Cyanomethyl)-4-(2-methylphenyl) piperidine-1-carboxylate. [1-(*tert*-Butoxycarbonyl)-4-(2-methylphenyl)piperidin-4-yl](cyano)acetic acid was subjected to the same decarboxylation conditions used in Example 16d and purified by chromatography on silica gel eluting with a 1:9 to 1:1 ethyl acetate:hexane gradient to give *tert*-butyl 4-(cyanomethyl)-4-(2-methylphenyl)piperidine-1-carboxylate as a solid (2.4 g, 76% overall yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (m, 1H), 7.19 (m, 3H), 3.72 (m, 2H), 3.15 (m, 2H), 2.76 (s, 2H), 2.50–2.55 (m, 2H), 2.48 (s, 3H), 1.93 (m, 2H), 1.44 (s, 9H). ES-LCMS *m/z* 337 (M+23).

tert-Butyl 4-(2-methylphenyl)-4-(2-oxoethyl)piperidine-1-carboxylate. Using the same procedure as in Example 16e using *tert*-butyl 4-

(cyanomethyl)-4-(2-methylphenyl) piperidine-1-carboxylate (2.4 g, 7.5 mmol) gave *tert*-butyl 4-(2-methylphenyl)-4-(2-oxoethyl)piperidine-1-carboxylate as a foam (1.6 g, 69%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.32 (t, 1H), 7.31 (m, 1H), 7.18 (m, 3H), 3.51–3.58 (m, 2H), 3.37–3.44 (m, 2H), 2.83 (s, 2H), 2.53 (s, 3H), 2.33 (m, 2H), 1.96 (m, 2H), 1.44 (s, 9H). ES-LCMS *m/z* 340 (M+23).

tert-Butyl 4-{2-[3-(2-Methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-(2-methylphenyl)piperidine-1-carboxylate. Using the same procedure as in Example 16f using *tert*-butyl 4-(2-methylphenyl)-4-(2-oxoethyl)piperidine-1-carboxylate (1.6 g, 5 mmol) gave *tert*-butyl 4-{2-[3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-(2-methylphenyl)piperidine-1-carboxylate as a solid (2.5 g, 94%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (m, 1H), 7.13–7.32 (m, 7H), 4.63 (m, 1H), 3.61 (m, 2H), 3.28 (m, 4H), 2.88 (m, 2H), 2.59 (s, 3H), 2.54 (s, 3H), 2.34-2.40 (m, 4H), 1.82–1.96 (m, 8H), 1.63 (m, 2H), 1.44 (s, 9H). ES-LCMS *m/z* 543 (M+1).

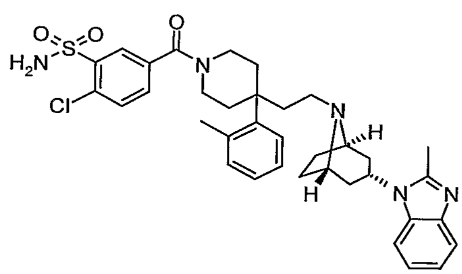
2-Methyl-1-(8-{2-[4-(2-methylphenyl) piperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-1H-benzimidazole Dihydrochloride. Using the same procedure as in Example 16g using *tert*-butyl 4-{2-[3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-(2-methylphenyl)piperidine-1-carboxylate (2.5 g, 4.6 mmol) gave 2-methyl-1-(8-{2-[4-(2-methylphenyl)piperidin-4-yl]ethyl}-8-azabicyclo[3.2.1] oct-3-yl)-1H-benzimidazole dihydrochloride as a solid (2.2 g, 100%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.28 (s, 1H), 9.02 (m, 2H), 7.89 (m, 1H), 7.80 (m, 1H), 7.55 (m, 2H), 7.20 (m, 4H), 6.05 (m, 1H), 4.11 (m, 2H), 3.26 (m, 2H), 3.05 (m, 1H), 2.88 (s, 4H), 2.81 (m, 3H), 2.53 (s, 3H), 2.33 (m, 2H), 2.13–2.23 (m, 8H), 2.08 (m, 2H). ES-LCMS *m/z* 443 (M+1).

1-((1R,5S)-8-{2-[1-(2,2-Dimethylpropanoyl)-4-(2-methylphenyl)piperidin-4-yl]ethyl}-8-azabicyclo [3.2.1]oct-3-yl)-2-methyl-1H-benzimidazole (example 655). A mixture of 2-methyl-1-(8-{2-[4-(2-methylphenyl)piperidin-4-yl]ethyl}-8-azabicyclo[3.2.1] oct-3-yl)-1H-benzimidazole dihydrochloride (0.15 g, 0.31 mmol), triethylamine (0.087 mL, 0.62 mmol) and trimethylacetyl chloride (0.043 mL, 0.34 mmol) in

dichloromethane (3 mL) was stirred at rt for 1h. The reaction mixture was diluted with dichloromethane, washed with saturated sodium bicarbonate solution, dried, concentrated and purified by chromatography on silica gel eluting with 33:1 dichloromethane:methanol to give 1-((1R,5S)-8-{2-[1-(2,2-dimethylpropanoyl)-4-(2-methylphenyl)piperidin-4-yl]ethyl}-8-azabicyclo [3.2.1]oct-3-yl)-2-methyl-1H-benzimidazole as a white solid (0.073 g, 45%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (m, 1H), 7.13–7.31 (m, 7H), 4.62 (m, 1H), 3.86 (m, 2H), 3.48 (m, 2H), 3.24 (m, 2H), 2.56 (m, 6H), 2.34 (m, 4H), 1.93 (m, 8H), 1.60 (m, 4H), 1.27 (s, 9H). HRMS $C_{34}H_{46}N_4O$ *m/z* 527.3750 $(M+H)_{Cal.}$, 527.3749 $(M+H)_{Obs.}$.

Example 656

2-Chloro-5-{[4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-(2-methylphenyl)piperidin-1-yl]carbonyl}benzenesulfonamide

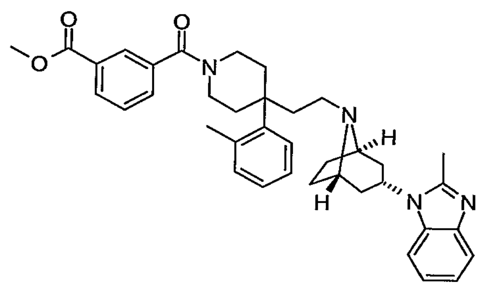


A mixture of 2-methyl-1-(8-{2-[4-(2-methylphenyl)piperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-1H-benzimidazole dihydrochloride (0.30 g, 0.63 mmol), 4-chloro-3-sulfamoylbenzoic acid (0.15 g, 0.63 mmol) and triethylamine (0.3 mL, 2 mmol) in dimethylformamide (2 mL) was treated with O-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (0.26 g, 0.69 mmol) and the resulting mixture was stirred for 1 h at rt. The mixture was diluted with water and the resulting precipitate was collected, washed with saturated sodium bicarbonate solution and water, dried and purified by chromatography on silica gel eluting with a gradient of 310:15:1 to 200:15:1 of chloroform:methanol:ammonium hydroxide to give 2-chloro-5-{[4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-

yl]ethyl}-4-(2-methylphenyl)piperidin-1-yl]carbonyl}benzenesulfonamide as a white solid (0.089 g, 21%). ^{1}H NMR (400 MHz, CD_3OD) δ 8.08 (s, 1H), 7.68 (m, 1H), 7.60 (m, 1H), 7.52 (m, 1H), 7.41 (m, 1H), 7.33 (m, 1H), 7.13–7.21 (m, 5H), 4.75 (m, 1H), 4.08 (m, 1H), 3.49 – 3.58 (m, 2H), 3.31 (m, 5H), 2.55 (m, 7H), 2.46 (m, 3H), 1.90–2.09 (m, 10H), 1.65 (m, 2H). HRMS $C_{36}H_{42}ClN_5O_3S$ *m/z* 660.2775 $(M+H)_{Cal.}$, 660.2764 $(M+H)_{Obs.}$.

Example 657

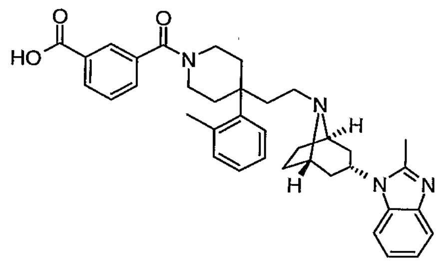
Methyl 3-{[4-{2-[(1R,5S)-3-(2-Methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-(2-methylphenyl)piperidin-1-yl]carbonyl}benzoate



A mixture of 2-methyl-1-(8-{2-[4-(2-methyl phenyl)piperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-1H-benzimidazole dihydrochloride (0.40 g, 0.84 mmol), monomethyl isophthalate (0.15 g, 0.84 mmol) and triethylamine (0.4 mL, 2.9 mmol) in dimethylformamide (3 mL) was treated with O-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (0.35 g, 0.92 mmol) and stirred at rt for 1 h. The mixture was diluted with water and the resultant precipitate was collected, washed with water, dried and purified by chromatography on silica gel eluting with 1:33 methanol:dichloromethane to give methyl 3-{[4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-(2-methylphenyl) piperidin-1-yl]carbonyl}benzoate as a glass (0.240 g, 47%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (m, 2H), 7.67 (m, 2H), 7.59 (m, 1H), 7.49 (t, 1H), 7.13–7.29 (m, 6H), 4.62 (m, 1H), 4.11 (m, 1H), 3.93 (s, 3H), 3.56 (m, 2H), 3.26 (m, 2H), 2.54 (m, 5H), 2.36 (m, 4H), 1.95 (m, 10H), 1.64 (m, 4H). HRMS $C_{38}H_{44}N_4O_3$ *m/z* 605.3492 $(M+H)_{Cal.}$ 605.3497 $(M+H)_{Obs.}$.

Example 658

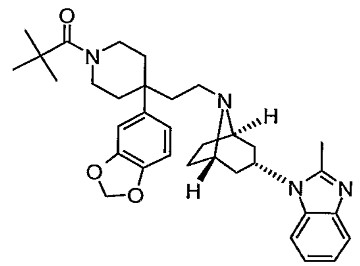
3-{[4-{2-[(1R,5S)-3-(2-Methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-(2-methylphenyl)piperidin-1-yl]carbonyl}benzoic Acid



A solution of methyl 3-{[4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-(2-methylphenyl)piperidin-1-yl]carbonyl} benzoate (0.15 g, 0.29 mmol) in methanol (1 mL) was treated with 2N sodium hydroxide solution (1.5 mL) and let stir at rt for 4 h. The mixture was concentrated to remove methanol and acidified by adding 1N hydrochloric acid. The resulting precipitate was collected, washed with water and dried to give 3-{[4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-(2-methylphenyl) piperidin-1-yl]carbonyl}benzoic acid as a pale pink solid (0.04 g, 31%). ^{1}H NMR (400 MHz, CD_3OD) δ 8.11 (m, 1H), 8.02 (s, 1H), 7.54 (m, 3H), 7.48 (m, 1H), 7.34 (m, 1H), 7.17–7.28 (m, 5H), 5.08 (m, 1H), 4.07 (m, 1H), 3.87 (m, 2H), 3.54 (m, 2H), 3.30 (m, 1H), 2.71 (m, 2H), 2.39–2.55 (m, 10H), 2.22–2.30 (m, 6H), 2.09 (m, 3H), 1.92 (m, 1H). HRMS $C_{37}H_{42}N_4O_3$ *m/z* 591.3335 $(M+H)_{Cal.}$, 591.3350 $(M+H)_{Obs.}$.

Example 659

1-((1R,5S)-8-{2-[4-(1,3-Benzodioxol-5-yl)-1-(2,2-dimethylpropanoyl)piperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1H-benzimidazole



tert-Butyl 4-(1,3-benzodioxol-5-yl)-4-(1-cyano-2-ethoxy-2-oxoethyl)piperidine-1-carboxylate. Using the same procedure as in Example 16b 4-bromo-1,2-(methylenedioxy)benzene (10.2 g, 51 mmol) was used in place of 1-chloro-3-iodobenzene and purified by chromatography on silica gel eluting with a 1:9 to 1:2 ethyl acetate:hexane gradient to give *tert*-butyl 4-(1,3-benzodioxol-5-yl)-4-(1-cyano-2-ethoxy-2-oxoethyl)piperidine-1-carboxylate as a foam (4.6 g, 65%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.80 (m, 3H), 5.96 (s, 2H), 4.01 (m, 2H), 3.90 (m, 2H), 3.53 (s, 1H), 2.88 (m, 2H), 2.41–2.51 (m, 2H), 1.94–2 02 (m, 2H), 1.43 (s, 9H), 1.08 (t, 3H). ES-LCMS *m/z* 415 (M-1).

[4-(1,3-Benzodioxol-5-yl)-1-(tert-butoxycarbonyl)piperidin-4-yl](cyano)acetic Acid. *tert*-Butyl 4-(1,3-benzodioxol-5-yl)-4-(1-cyano-2-ethoxy-2-oxoethyl)piperidine-1-carboxylate (4.6 g, 11 mmol) was hydrolysed using the same procedure as in Example 16c to give [4-(1,3-benzodioxol-5-yl)-1-(tert-butoxycarbonyl)piperidin-4-yl](cyano)acetic acid as an amber foam (4.2 g, 100%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.82 (m, 3H), 5.97 (s, 2H), 3.88 (m, 2H), 3.55 (s, 1H), 2.88 (m, 2H), 2.48 (m, 2H), 1.89–2.03 (m, 2H), 1.41 (s, 9H). ES-LCMS *m/z* 387 (M-1).

tert-Butyl 4-(1,3-benzodioxol-5-yl)-4-(cyano methyl)piperidine-1-carboxylate. [4-(1,3-Benzodioxol-5-yl)-1-(tert-butoxycarbonyl)piperidin-4-yl](cyano) acetic acid (4.2 g, 11 mmol) was subjected to the same decarboxylation conditions used in Example 16d and purified by chromatography on silica gel eluting with a 1:9 to 1:2 ethyl acetate:hexane gradient to give *tert*-butyl 4-(1,3-benzodioxol-5-yl)-4-(cyanomethyl) piperidine-

1-carboxylate as a foam (2.9 g, 80%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.82 (m, 3H), 5.97 (s, 2H), 3.74 (m, 2H), 3.07 (m, 2H), 2.50 (s, 2H), 2.21 (m, 2H), 1.76–1.83 (m, 2H), 1.43 (s, 9H). ES-LCMS *m/z* 245 (M-99).

tert-Butyl 4-(1,3-benzodioxol-5-yl)-4-(2-oxoethyl)piperidine-1-carboxylate. Using the same procedure as in Example 16e *tert*-butyl 4-(1,3-benzodioxol-5-yl)-4-(cyanomethyl)piperidine-1-carboxylate (2.9 g, 8.6 mmol) gave *tert*-butyl 4-(1,3-benzodioxol-5-yl)-4-(2-oxoethyl)piperidine-1-carboxylate (2.0 g, 69%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.39 (t, 1H), 6.79–6.84 (m, 3H), 5.96 (s, 2H), 3.57–3.63 (m, 2H), 3.21–3.27 (m, 2H), 2.58 (s, 2H), 2.10–2.16 (m, 2H), 1.77–1.84 (m, 2H), 1.43 (s, 9H).

tert-Butyl 4-(1,3-benzodioxol-5-yl)-4-{2-[3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidine-1-carboxylate. Using the same procedure as in Example 16f *tert*-butyl 4-(1,3-benzodioxol-5-yl)-4-(2-oxoethyl)piperidine-1-carboxylate (2.0 g, 5.8 mmol) gave *tert*-butyl 4-(1,3-benzodioxol-5-yl)-4-{2-[3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidine-1-carboxylate after chromatography on silica gel eluting with a dichloromethane to 1:9 methanol:dichloromethane gradient as a foam (2.4 g, 73%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (m, 1H), 7.28 (m, 1H), 7.12–7.20 (m, 2H), 6.79 (m, 2H), 6.72 (m, 1H), 5.96 (s, 2H), 4.64 (m, 2H), 3.63 (m, 2H), 3.30 (m, 2H), 3.19 (m, 4H), 2.60 (s, 3H), 2.43 (m, 2H), 1.71–2.08 (m, 11H), 1.44 (s, 9H). ES-LCMS *m/z* 573 (M+1).

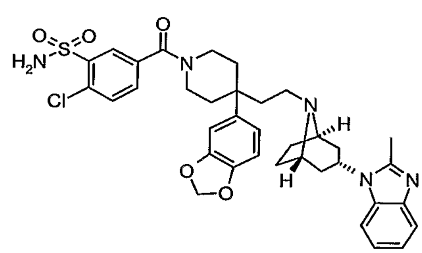
1-(8-{2-[4-(1,3-Benzodioxol-5-yl)piperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1H-benzimidazole dihydrochloride. Using the same procedure as in Example 16g *tert*-butyl 4-(1,3-benzo-dioxol-5-yl)-4-{2-[3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidine-1-carboxylate (2.4 g, 4.2 mmol) gave 1-(8-{2-[4-(1,3-benzodioxol-5-yl)piperidin-4-yl]ethyl}-8-azabicyclo [3.2.1]oct-3-yl)-2-methyl-1H-benzimidazole dihydro-chloride as a solid (2.1 g, 100%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.22 (s, 1H), 9.06–9.13 (m, 2H), 7.88 (m, 1H), 7.80 (m, 1H), 7.56 (m, 2H), 7.02 (s, 1H), 6.91 (m, 1H), 6.82 (m, 1H), 6.02 (s, 2H), 4.07

(m, 2H), 3.19 (m, 2H), 2.88 (s, 3H), 2.78–2.83 (m, 4H), 2.52 (m, 2H), 1.95–2.26 (m, 11H). ES-LCMS *m/z* 473 (M+1).

Title compound in example 659. A mixture of 1-(8-{2-[4-(1,3-benzodioxol-5-yl)piperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1H-benzimidazole dihydrochloride (0.2 g, 0.39 mmol), triethylamine (0.11 mL, 0.78 mmol) and trimethylacetyl chloride (0.053 mL, 0.43 mmol) in dichloromethane (4 mL) was stirred at rt for 1 h before the reaction mixture was quenched with saturated sodium bicarbonate solution. The organic layer was separated, dried and concentrated to give 1-((1R,5S)-8-{2-[4-(1,3-benzodioxol-5-yl)-1-(2,2-dimethylpropanoyl)piperidin-4-yl]ethyl}-8-azabicyclo [3.2.1]oct-3-yl)-2-methyl-1H-benzimidazole as a foam (0.18 g, 82%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (m, 1H), 7.29 (m, 3H), 6.83 (m, 2H), 6.75 (m, 1H), 6.21 (m, 1H), 6.00 (s, 2H), 3.95 (m, 2H), 3.84 (m, 2H), 3.38 (m, 2H), 2.98 (m, 2H), 2.86 (s, 3H), 2.56 (m, 2H), 2.31 (m, 4H), 2.07–2.21 (m, 4H), 1.82 (m, 4H), 1.26 (s, 9H). HRMS $C_{34}H_{44}N_4O_3$ *m/z* 557.3492 $(M+H)_{Cal.}$, 557.3495 $(M+H)_{Obs.}$.

Example 660

5-[(4-(1,3-Benzodioxol-5-yl)-4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)carbonyl]-2-chlorobenzene sulfonamide

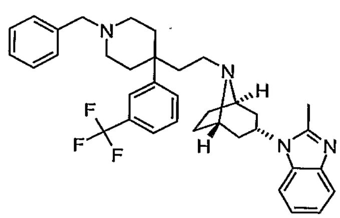


A mixture of 1-(8-{2-[4-(1,3-benzodioxol-5-yl)piperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1H-benzimidazole dihydrochloride (0.40 g, 0.78 mmol), triethylamine (0.35 mL, 2.5 mmol) and 4-chloro-3-sulfamoylbenzoic acid (184 mg, 0.78 mmol) in dimethylformamide (2.5 mL) was treated with O-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (327 mg, 0.86 mmol) and the resulting mixture was

stirred for 1 h at rt. The mixture was diluted with water and the resulting precipitate was collected, washed with saturated sodium bicarbonate solution and water, dried and purified by chromatography on silica gel eluting with a chloroform:methanol:ammonium hydroxide 400:15:1 to 200:15:1 gradient to give 5-[(4-(1,3-benzodioxol-5-yl)-4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl) carbonyl]-2-chlorobenzenesulfonamide as a solid (0.09 g, 17%). ^{1}H NMR (400 MHz, CD_3OD) δ 8.08 (s, 1H), 7.67 (m, 1H), 7.59 (m, 1H), 7.51 (m, 1H), 7.41 (m, 1H), 7.17 (m, 2H), 6.94 (s, 1H), 6.81–6.86 (m, 2H), 5.93 (s, 2H), 4.74 (m, 1H), 4.11 (m, 1H), 3.52 (m, 1H), 3.30 (m, 4H), 2.52 (s, 3H), 2.44 (m, 2H), 2.39 (m, 1H), 2.18 (m, 1H), 1.80–2.04 (m, 12H), 1.70 (m, 2H). HRMS $C_{36}H_{40}ClN_5O_5$ *m/z* 690.2517 $(M+H)_{Cal.}$, 690.2538 $(M+H)_{Obs.}$.

Example 661

1-[(1R,5S)-8-(2-{1-Benzyl-4-[3-(trifluoromethyl)phenyl] piperidin-4-yl}ethyl)-8-azabicyclo[3.2.1]oct-3-yl]-2-methyl-1H-benzimidazole



The following compounds were prepared according to the procedures in Example 16.

Ethyl (1-Benzylpiperidin-4-ylidene)(cyano)acetate. Using the same procedure as in Example 16a 1-benzylpiperidin-4-one (47.3 g, 0.25 mol) was used in place of *tert*-butyl 4-oxo-1-piperidine carboxylate to give ethyl (1-benzylpiperidin-4-ylidene)(cyano)acetate as a solid (72.2 g, 100%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25–7.35 (m, 5H), 4.26 (q, 2H), 3.54 (s, 2H), 3.14 (m, 2H), 2.78 (m, 2H), 2.64 (m, 2H), 2.59 (m, 2H), 1.33 (t, 3H). ES-LCMS *m/z* 283 (M-1).

Ethyl {1-Benzyl-4-[3-(trifluoromethyl)phenyl] piperidin-4-yl}(cyano)acetate. Using the same procedure as in Example 16b 3-

bromobenzotrifluoride (20.2 g, 0.09 mol) was used in place of 1-chloro-3-iodobenzene to give ethyl {1-benzyl-4-[3-(trifluoro methyl)phenyl]piperidin-4-yl}(cyano)acetate as a solid (5.6 g, 37%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51–7.63 (m, 4H), 7.22–7.35 (m, 5H), 3.92 (m, 2H), 3.69 (s, 1H), 3.40 (s, 2H), 2.67 (m, 2H), 2.51 (m, 2H), 2.18–2.29 (m, 4H), 0.99 (t, 3H). ES-LCMS *m/z* 431 (M+1).

{1-Benzyl-4-[3-(trifluoromethyl)phenyl] piperidin-4-yl}(cyano)acetic Acid. Ethyl {1-benzyl-4-[3-(trifluoromethyl)phenyl]piperidin-4-yl}(cyano) acetate (5.6 g, 0.013 mol) was hydrolysed using the same procedure as in Example 16c to give an amber foam (5.2 g, 100%) that was used without further purification.

{1-Benzyl-4-[3-(trifluoromethyl)phenyl] piperidin-4-yl}acetonitrile. {1-Benzyl-4-[3-(trifluoromethyl)phenyl]piperidin-4-yl}(cyano)acetic acid (5.2 g, 0.013 mol) was subjected to the same decarboxylation conditions used in Example 16d and purified by column chromatography on silica gel eluting with 1:1 hexane:ethyl acetate to give {1-benzyl-4-[3-(trifluoromethyl)phenyl]piperidin-4-yl}acetonitrile as a solid (2.9 g, 63%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51–7.58 (m, 4H), 7.25–7.36 (m, 5H), 3.49 (s, 2H), 2.60 (m, 4H), 2.35 (m, 4H), 2.10 (s, 2H). ES-LCMS *m/z* 359 (M+1).

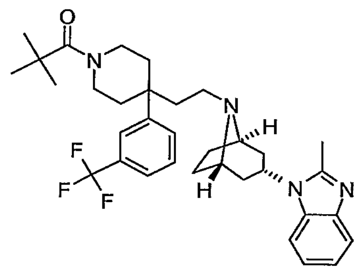
{1-Benzyl-4-[3-(trifluoromethyl)phenyl] piperidin-4-yl}acetaldehyde. Using the same procedure as in Example 16e {1-benzyl-4-[3-(trifluoromethyl) phenyl]piperidin-4-yl}acetonitrile (2.4 g, 6.7 mmol) gave {1-benzyl-4-[3-(trifluoromethyl)phenyl]piperidin-4-yl}acetaldehyde as a tan foam (2.0 g, 83%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.38 (t, 1H), 7.48–7.60 (m, 4H), 7.25–7.32 (m, 5H), 3.45 (s, 2H), 2.70 (s, 2H), 2.56 (m, 2H), 2.38 (m, 2H), 2.25 (m, 2H), 2.01 (m, 2H). ES-LCMS m/z 360 (M-1).

Title compound in example 661: 1-[(1R,5S)-8-(2-{1-Benzyl-4-[3-(trifluoromethyl)phenyl]piperidin-4-yl}ethyl)-8-azabicyclo[3.2.1]oct-3-yl]-2-methyl-1H-benzimidazole. Using the same procedure as in Example 16f {1-benzyl-4-[3-(trifluoromethyl)phenyl]piperidin-4-yl}acetaldehyde (0.23 g, 0.64 mmol) was used in place of *tert*-butyl 4-(3-chlorophenyl)-4-(2-oxoethyl) piperidine-1-carboxylate to give 1-[(1R,5S)-8-(2-{1-benzyl-4-[3-(trifluoromethyl)phenyl]piperidin-4-yl}ethyl)-8-azabicyclo[3.2.1]oct-3-yl]-2-

methyl-1H-benzimidazole as a glass (0.10 g, 27%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (m, 1H), 7.55 (s, 1H), 7.49 (s, 3H), 7.26–7.33 (m, 6H), 7.12–7.20 (m, 2H), 4.63 (m, 1H), 3.53 (m, 2H), 3.25 (m, 2H), 2.72 (m, 2H), 2.56 (s, 3H), 2.38 (m, 4H), 2.24 (m, 2H), 1.84–1.94 (m, 10H), 1.63 (m, 2H). HRMS $C_{36}H_{41}F_3N_4$ *m/z* 587.3362 $(M+H)_{Cal.}$, 587.3375 $(M+H)_{Obs.}$.

Example 662

1-[(1R,5S)-8-(2-{1-(2,2-Dimethylpropanoyl)-4-[3-(trifluoromethyl)phenyl]piperidin-4-yl}ethyl)-8-azabicyclo[3.2.1]oct-3-yl]-2-methyl-1H-benzimidazole



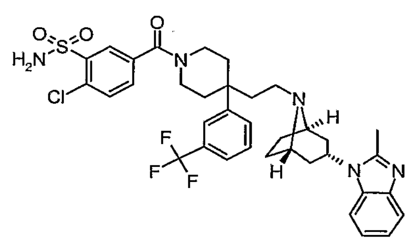
2-Methyl-1-[8-(2-{4-[3-(trifluoromethyl) phenyl]piperidin-4-yl}ethyl)-8-azabicyclo[3.2.1]oct-3-yl]-1H-benzimidazole dihydrochloride. A mixture of 1-[(1R,5S)-8-(2-{1-benzyl-4-[3-(trifluoromethyl)phenyl] piperidin-4-yl}ethyl)-8-azabicyclo[3.2.1]oct-3-yl]-2-methyl-1H-benzimidazole (0.2 g, 0.34 mmol), 1N hydrochloric acid (0.34 mL) and 10% Palladium on carbon (50 mg) in methanol (10 mL) was hydrogenated overnight at rt and atmospheric pressure. The mixture was filtered through celite and concentrated to give 2-methyl-1-[8-(2-{4-[3-(trifluoromethyl)phenyl] piperidin-4-yl}ethyl)-8-azabicyclo[3.2.1]oct-3-yl]-1H-benzimidazole dihydrochloride as a solid (0.15 g, 89%) that was used without further purification.

Title compound in example 662: *1-[(1R,5S)-8-(2-{1-(2,2-Dimethylpropanoyl)-4-[3-(trifluoromethyl) phenyl]piperidin-4-yl}ethyl)-8-azabicyclo[3.2.1]oct-3-yl]-2-methyl-1H-benzimidazole.* A mixture of 2-methyl-1-[8-(2-{4-[3-(trifluoromethyl)phenyl]piperidin-4-yl}ethyl)-8-azabicyclo[3.2.1]oct-3-yl]-1H-benzimidazole dihydrochloride (0.05 g, 0.1 mmol), triethylamine (0.028 mL, 0.2 mmol) and trimethylacetyl chloride (0.014

mL, 0.11 mmol) in dichloromethane (1 mL) was stirred 1 h at rt before the reaction mixture was quenched with saturated sodium bicarbonate solution. The organic layer was separated, dried, concentrated and purified by chromatography on silica gel eluting with 1:33 methanol:dichloromethane to give 1-[(1R,5S)-8-(2-{1-(2,2-dimethylpropanoyl)-4-[3-(trifluoro methyl)phenyl]piperidin-4-yl}ethyl)-8-azabicyclo[3.2.1] oct-3-yl]-2-methyl-1H-benzimidazole as a glass (0.025 g, 43%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (m, 1H), 7.54 (m, 4H), 7.13–7.21 (m, 3H), 4.62 (m, 1H), 3.95 (m, 2H), 3.25 – 3.37 (m, 3H), 2.61 (s, 3H), 2.40 (m, 2H), 2.18 (m, 3H), 1.88 (m, 10H), 1.64 (m, 2H), 1.27 (s, 9H). HRMS $C_{34}H_{43}F_3ON_4$ *m/z* 581.3467 $(M+H)_{Cal.}$, 581.3476 $(M+H)_{Obs.}$.

Example 663

2-Chloro-5-({4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-[3-(tri-fluoromethyl)phenyl]piperidin-1-yl}carbonyl)benzene-sulfonamide

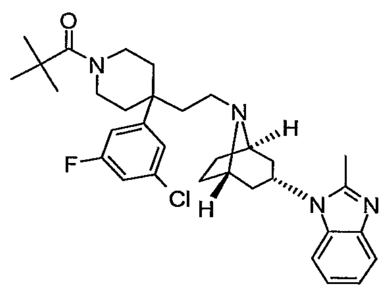


A mixture of 2-methyl-1-[8-(2-{4-[3-(trifluoromethyl)phenyl]piperidin-4-yl}ethyl)-8-azabicyclo[3.2.1]oct-3-yl]-1H-benzimidazole dihydrochloride (0.1 g, 0.2 mmol), triethylamine (0.056 mL, 0.4 mmol) and 3-(aminosulfonyl)-4-chlorobenzoyl chloride (0.056 g, 0.22 mmol) in dichloromethane (2 mL) was stirred at rt for 1.5 h. The reaction mixture was diluted with dichloromethane, washed with saturated sodium bicarbonate solution, dried, concentrated and purified by three successive chromatographies on silica gel eluting with mixtures of methanol in dichloromethane to give 2-chloro-5-({4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-[3-(trifluoromethyl)phenyl]piperidin-1-yl}carbonyl)benzenesulfonamide as a wax (0.002 g, 2%). ^{1}H NMR (400 MHz, CD_3OD_3) δ 7.79–7.94 (m, 2H), 7.57–7.71

(m, 5H), 7.40–7.54 (m, 2H), 7.15–7.21 (m, 2H), 4.73 (m, 1H), 4.15 (m, 1H), 3.39–3.55 (m, 4H), 3.16–3.22 (m, 1H), 2.52 (s, 3H), 2.34–2.50 (m, 3H), 2.22–2.32 (m, 1H), 1.94–2.12 (m, 10H), 1.68–1.74 (m, 2H). HRMS $C_{36}H_{39}ClF_3N_5O_3S$ *m/z* 714.2492 $(M+H)_{Cal.}$, 714.2496 $(M+H)_{Obs.}$.

Example 664

1-((1R,5S)-8-{2-[4-(3-Chloro-5-fluorophenyl)-1-(2,2-dimethylpropanoyl)piperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1H-benzimidazole



tert-Butyl 4-(3-chloro-5-fluorophenyl)-4-(1-cyano-2-ethoxy-2-oxoethyl)piperidine-1-carboxylate. Using the same procedure as in Example 16b 1-bromo-3-chloro-5-fluorobenzene (10.7 g, 51 mmol) was used in place of 1-chloro-3-iodobenzene to give *tert*-butyl 4-(3-chloro-5-fluorophenyl)-4-(1-cyano-2-ethoxy-2-oxoethyl)piperidine-1-carboxylate as an amber foam that was used without further purification.

[1-(tert-Butoxycarbonyl)-4-(3-chloro-5-fluorophenyl)piperidin-4-yl](cyano)acetic Acid. *tert*-Butyl 4-(3-chloro-5-fluorophenyl)-4-(1-cyano-2-ethoxy-2-oxoethyl)piperidine-1-carboxylate was hydrolysed using the same procedure as in Example 16c to give [1-(*tert*-butoxycarbonyl)-4-(3-chloro-5-fluorophenyl) piperidin-4-yl](cyano)acetic acid as an amber foam that was used without further purification.

tert-Butyl 4-(3-chloro-5-fluorophenyl)-4-(cyanomethyl)piperidine-1-carboxylate. [1-(*tert*-Butoxycarbonyl)-4-(3-chloro-5-fluorophenyl)piperidin-4-yl](cyano)acetic acid was subjected to the same decarboxylation conditions used in Example 16d and purified by chromatography on silica gel eluting with 1:4 ethyl acetate:hexane to give *tert*-butyl 4-(3-chloro-5-fluorophenyl)-4-

(cyanomethyl)piperidine-1-carboxylate as a solid (2.3 g, 38% overall). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.13 (s, 1H), 7.05 (m, 1H), 6.98 (m, 1H), 3.71 (m, 2H), 3.11 (m, 2H), 2.55 (s, 2H), 2.20 (m, 2H), 1.86 (m, 2H), 1.43 (s, 9H). ES-LCMS *m/z* 253 (M-99).

tert-Butyl 4-(3-chloro-5-fluorophenyl)-4-(2-oxoethyl)piperidine-1-carboxylate. Using the same procedure as in Example 16e *tert*-butyl 4-(3-chloro-5-fluorophenyl)-4-(cyanomethyl)piperidine-1-carboxylate (2.3 g, 6.5 mmol) gave *tert*-butyl 4-(3-chloro-5-fluorophenyl)-4-(2-oxoethyl)piperidine-1-carboxylate as an amber foam (1.5 g, 65%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.43 (t, 1H), 7.12 (s, 1H), 6.95–7.01 (m, 2H), 3.55–3.62 (m, 2H), 3.24–3.30 (m, 2H), 2.63 (s, 2H), 2.04–2.17 (m, 2H), 1.80–1.91 (m, 2H), 1.42 (s, 9H). ES-LCMS *m/z* 354 (M-1).

tert-Butyl 4-(3-chloro-5-fluorophenyl)-4-{2-[3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1] oct-8-yl]ethyl}piperidine-1-carboxylate. Using the same procedure as in Example 16f *tert*-butyl 4-(3-chloro-5-fluorophenyl)-4-(2-oxoethyl)piperidine-1-carboxylate (1.5 g, 4.2 mmol) gave *tert*-butyl 4-(3-chloro-5-fluorophenyl)-4-{2-[3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidine-1-carboxylate as a solid (1.7 g, 71%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (m, 1H), 7.29 (m, 1H), 7.17 (m, 2H), 7.08 (s, 1H), 6.98 (m, 1H), 6.91 (m, 1H), 4.66 (m, 2H), 3.83 (m, 2H), 3.62 (m, 2H), 3.25 (4H), 3.01 (m, 1H), 2.60 (s, 3H), 2.44 (m, 2H), 2.02 (m, 4H), 1.71–1.86 (m, 6H), 1.43 (s, 9H). ES-LCMS *m/z* 581 (M+1).

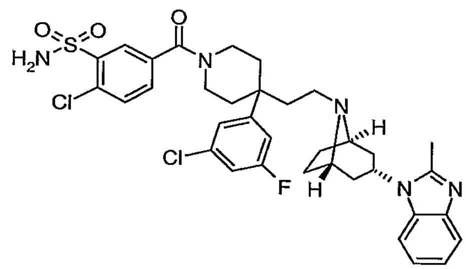
1-((1R,5S)-8-{2-[4-(3-Chloro-5-fluorophenyl) piperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1H-benzimidazole dihydrochloride. Using the same procedure as in Example 16g *tert*-butyl 4-(3-chloro-5-fluorophenyl)-4-{2-[3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl} piperidine-1-carboxylate (1.7g, 2.9 mmol) gave 1-((1*R*,5*S*)-8-{2-[4-(3-chloro-5-fluorophenyl)piperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1*H*-benzimidazole dihydrochloride as a solid (1.5 g, 100%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.26 (s, 1H), 9.14 (s, 2H), 7.89 (m, 1H), 7.80 (m, 1H), 7.55 (m, 2H), 7.37 (m, 1H), 7.30 (m, 2H), 6.03 (m, 1H), 4.11 (m, 2H), 3.22 (m, 2H),

3.11 (m, 1H), 2.88 (s, 3H), 2.75–2.90 (m, 4H), 2.30 (m, 2H), 2.10–2.25 (m, 8H), 2.08 (m, 2H). ES-LCMS *m/z* 481 (M+1).

1-((1R,5S)-8-{2-[4-(3-Chloro-5-fluorophenyl)-1-(2,2-dimethylpropanoyl)piperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1H-benzimidazole (example 664). A mixture of 1-((1*R*,5*S*)-8-{2-[4-(3-chloro-5-fluorophenyl)piperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1*H*-benzimidazole dihydrochloride (0.2 g, 0.39 mmol), triethylamine (0.11 mL, 0.78 mmol) and trimethylacetyl chloride (0.053 mL, 0.43 mmol) in dichloromethane (4 mL) was stirred at rt for 1 h before the reaction mixture was quenched with saturated sodium bicarbonate solution. The organic layer was separated, dried, concentrated and purified by two successive chromatographies on silica gel using a dichloromethane to methanol:dichloromethane 1:20 gradient to give 1-((1R,5S)-8-{2-[4-(3-chloro-5-fluorophenyl)-1-(2,2-dimethylpropanoyl)piperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1H-benzimidazole as a glass (0.06 g, 27%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (m, 1H), 7.29 (m, 1H), 7.17 (m, 2H), 7.09 (m, 1H), 7.00 (m, 1H), 6.93 (m, 1H), 4.72 (m, 1H), 3.90 (m, 2H), 3.37 (m, 4H), 2.61 (s, 3H), 2.47 (m, 2H), 1.89–2.11 (m, 8H), 1.78 (m, 6H), 1.27 (s, 9H). HRMS $C_{33}H_{42}ClFN_4O$ *m/z* 565.3109 $(M+H)_{Cal.}$, 565.3095 $(M+H)_{Obs.}$.

Example 665

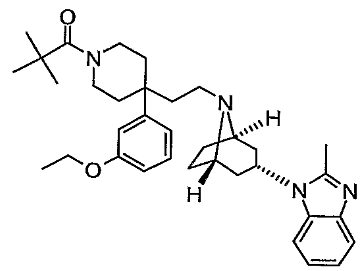
2-Chloro-5-[(4-(3-chloro-5-fluorophenyl)-4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo [3.2.1]oct-8-yl]ethyl}piperidin-1-yl)carbonyl]benzene sulfonamide



A mixture of 1-((1*R*,5*S*)-8-{2-[4-(3-chloro-5-fluorophenyl)piperidin-4-yl]ethyl}-8-azabicyclo[3.2.1] oct-3-yl)-2-methyl-1*H*-benzimidazole dihydrochloride (0.40 g, 0.78 mmol), triethylamine (0.35 mL, 2.5 mmol) and 4-chloro-3-sulfamoylbenzoic acid (184 mg, 0.78 mmol) in dimethylformamide (2.5 mL) was treated with O-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (327 mg, 0.86 mmol) and the resulting mixture was stirred for 1 h at rt. The mixture was diluted with water and the resulting precipitate was collected, washed with saturated sodium bicarbonate solution and water, dried and purified by chromatography on silica gel eluting with a gradient of chloroform:methanol:ammonium hydroxide 400:15:1 to 200:15:1 to give 2-chloro-5-[(4-(3-chloro-5-fluoro phenyl)-4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)carbonyl]benzenesulfonamide as a solid (0.20 g, 36%). ^{1}H NMR (400 MHz, CD_3OD) δ 8.09 (s, 1H), 7.67 (m, 1H), 7.60 (m, 1H), 7.51 (m, 1H), 7.42 (m, 1H) 7.30 (s, 1H), 7.10–7.21 (m, 4H), 4.72 (m, 1H), 4.06 (m, 1H), 3.57 (m, 1H), 3.47 (m, 1H), 3.30 (m, 3H), 2.52 (s, 3H), 2.40–2.48 (m, 4H), 2.27 (m, 1H), 2.14 (m, 1H), 1.83–2.04 (m, 10H), 1.70 (m, 2H). HRMS $C_{35}H_{38}Cl_2FN_5O_3S$ *m/z* 698.2134 $(M+H)_{Cal.}$, 698.2161 $(M+H)_{Obs.}$.

Example 666

1-((1R,5S)-8-{2-[1-(2,2-Dimethylpropanoyl)-4-(3-ethoxyphenyl)piperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1H-benzimidazole



tert-Butyl 4-(1-cyano-2-ethoxy-2-oxoethyl)-4-(3-ethoxyphenyl)piperidine-1-carboxylate. Using the same procedure as in Example 16b 3-bromophenetole (10.2 g, 51 mmol) was used in place of 1-chloro-3-iodobenzene and purified by chromatography on silica gel eluting with a 1:9 to 1:2 ethyl acetate:hexane gradient to give *tert*-butyl 4-(1-cyano-2-ethoxy-2-oxoethyl)-4-(3-ethoxyphenyl)piperidine-1-carboxylate as an oil (5.4 g, 77%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 (m, 1H), 6.81–6.91 (m, 3H), 3.90–4.04 (m, 4H), 3.55 (s, 1H), 2.86 (m, 2H), 2.54 (m, 2H), 1.95–2.05 (m, 4H), 1.43 (s, 9H), 1.40 (t, 3H), 1.04 (t, 3H). ES-LCMS *m/z* 317 (M-99).

[1-(tert-Butoxycarbonyl)-4-(3-ethoxyphenyl)piperidin-4-yl](cyano)acetic Acid. *tert*-Butyl 4-(1-cyano-2-ethoxy-2-oxoethyl)-4-(3-ethoxy phenyl)piperidine-1-carboxylate was hydrolysed using the same procedure as in Example 16c to give [1-(*tert*-butoxycarbonyl)-4-(3-ethoxyphenyl)piperidin-4-yl](cyano)acetic acid as a pale yellow foam that was used without further purification.

tert-Butyl 4-(cyanomethyl)-4-(3-ethoxyphenyl) piperidine-1-carboxylate. [1-(*tert*-Butoxycarbonyl)-4-(3-ethoxyphenyl)piperidin-4-yl](cyano)acetic acid was subjected to the same decarboxylation conditions used in Example 16d and purified by chromatography on silica gel eluting with a 1:9 to 1:2 ethyl acetate:hexane gradient to give *tert*-butyl 4-(cyanomethyl)-4-(3-ethoxyphenyl)piperidine-1-carboxylate as a solid (3.1 g, 72%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (m, 1H), 6.80–6.94 (m, 3H), 4.04 (m, 2H), 3.74–3.80 (m,

2H), 3.06 (m, 2H), 2.53 (s, 2H), 2.30 (m, 2H), 1.83 (m, 2H), 1.43 (s, 9H), 1.40 (t, 3H). ES-LCMS *m/z* 245 (M-99).

tert-Butyl 4-(3-ethoxyphenyl)-4-(2-oxoethyl) piperidine-1-carboxylate. Using the same procedure as in Example 16e *tert*-butyl 4-(cyanomethyl)-4-(3-ethoxyphenyl)piperidine-1-carboxylate (3.1 g, 9 mmol) gave *tert*-butyl 4-(3-ethoxyphenyl)-4-(2-oxoethyl) piperidine-1-carboxylate as a solid (2.1 g, 68%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.37 (t, 1H), 7.30 (m, 1H), 6.89 –6.92 (m, 2H), 6.76 (m, 1H), 4.02 (m, 2H), 3.59–3.65 (m, 2H), 3.19–3.26 (m, 2H), 2.60 (s, 2H), 2.17–2.22 (m, 2H), 1.85 (m, 2H), 1.43 (s, 9H), 1.40 (m, 3H).

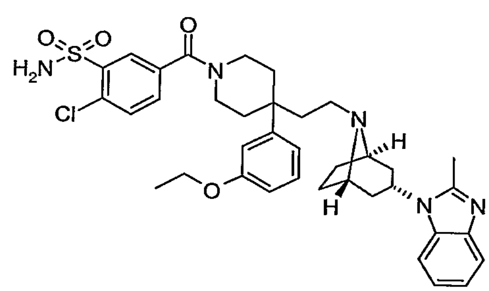
tert-Butyl 4-(3-ethoxyphenyl)-4-{2-[3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidine-1-carboxylate. Using the same procedure as in Example 16f *tert*-butyl 4-(3-ethoxy phenyl)-4-(2-oxoethyl)piperidine-1-carboxylate (2.1 g, 6 mmol) gave *tert*-butyl 4-(3-ethoxyphenyl)-4-{2-[3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidine-1-carboxylate after chromatography on silica gel eluting with a dichloromethane to 1:9 methanol:dichloromethane gradient as a solid (3.0 g, 88%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (m, 1H), 7.26 (m, 2H), 7.13–7.19 (m, 2H), 6.85 (m, 2H), 6.75 (m, 1H), 4.66 (m, 2H), 4.03 (m, 2H), 3.65 (m, 2H), 3.30 (m, 2H), 3.17 (m, 4H), 2.60 (s, 3H), 2.40 (m, 2H), 1.65–2.16 (m, 11H), 1.43 (s, 9H), 1.40 (m, 3H). ES-LCMS *m/z* 573 (M+1).

1-(8-{2-[4-(3-Ethoxyphenyl)piperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1H-benzimidazole dihydrochloride. Using the same procedure as in Example 16g *tert*-butyl 4-(3-ethoxy phenyl)-4-{2-[3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidine-1-carboxylate (3.0 g, 5.2 mmol) gave 1-(8-{2-[4-(3-ethoxyphenyl)piperidin-4-yl]ethyl}-8-azabicyclo[3.2.1] oct-3-yl)-2-methyl-1H-benzimidazole dihydrochloride as a solid (2.6 g, 100%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.21 (s, 1H), 9.04 (s, 2H), 7.88 (m, 1H), 7.80 (m, 1H), 7.55 (m, 2H), 7.31 (m, 1H), 6.83–6.94 (m, 3H), 6.02 (m, 1H), 4.07 (m, 2H), 3.21 (m, 2H), 2.88 (s, 3H), 2.75–2.83 (m, 4H), 2.52 (m, 2H), 2.18–2.34 (m, 8H), 2.08 (m, 4H), 1.33 (t, 3H). ES-LCMS *m/z* 473 (M+1).

1-((1R,5S)-8-{2-[1-(2,2-Dimethylpropanoyl)-4-(3-ethoxyphenyl)piperidin-4-yl]ethyl}-8-azabicyclo [3.2.1]oct-3-yl)-2-methyl-1H-benzimidazole (example 666). A mixture of 1-(8-{2-[4-(3-ethoxyphenyl) piperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1H-benzimidazole dihydrochloride (0.2 g, 0.39 mmol), triethylamine (0.11 mL, 0.78 mmol) and trimethylacetyl chloride (0.053 mL, 0.43 mmol) in dichloromethane (4 mL) was stirred at rt for 1 h before the reaction mixture was quenched with saturated sodium bicarbonate solution. The organic layer was separated, dried, concentrated and purified by chromatography on silica gel eluting with a dichloromethane to 1:9 methanol:dichloromethane gradient to give 1-((1R,5S)-8-{2-[1-(2,2-dimethylpropanoyl)-4-(3-ethoxyphenyl) piperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1H-benzimidazole as a foam (0.14 g, 65%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (m, 1H), 7.28 (m, 2H), 7.16 (m, 2H), 6.86 (m, 2H), 6.76 (m, 1H), 4.63 (m, 1H), 4.04 (m, 2H), 3.94 (m, 2H), 3.29 (m, 4H), 2.59 (s, 3H), 2.40 (m, 2H), 2.19 (m, 2H), 1.66–1.95 (m, 12H), 1.43 (t, 3H), 1.26 (s, 9H). HRMS $C_{35}H_{48}N_4O_2$ *m/z* 557.3856 $(M+H)_{Cal.}$, 557.3840 $(M+H)_{Obs.}$.

Example 667

2-Chloro-5-[(4-(3-ethoxyphenyl)-4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)carbonyl]benzenesulfonamide

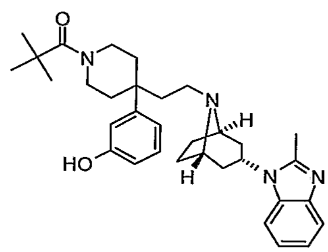


A mixture of 1-(8-{2-[4-(3-ethoxyphenyl) piperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1H-benzimidazole dihydrochloride (0.40 g, 0.78 mmol), triethylamine (0.35 mL, 2.5 mmol) and 4-chloro-3-sulfamoylbenzoic acid (184 mg, 0.78 mmol) in dimethylformamide (2.5 mL)

was treated with O-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (327 mg, 0.86 mmol) and the resulting mixture was stirred for 1 h at rt. The mixture was diluted with water and the resulting precipitate was collected, washed with saturated sodium bicarbonate solution and water, dried and purified by chromatography on silica gel eluting with a chloroform:methanol:ammonium hydroxide 400:15:1 to 200:15:1 gradient to give 2-chloro-5-[(4-(3-ethoxy phenyl)-4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)carbonyl]benzenesulfonamide as a solid (0.34 g, 62%). ^{1}H NMR (400 MHz, CD_3OD) δ 8.08 (s, 1H), 7.67 (m, 1H), 7.59 (m, 1H), 7.51 (m, 1H), 7.41 (m, 1H), 7.29 (m, 1H), 7.17 (m, 2H), 6.93–6.98 (m, 2H), 6.81 (m, 1H), 4.74 (m, 1H), 4.17 (m, 1H), 4.04 (m, 2H), 3.54 (m, 1H), 3.30 (m, 4H), 2.52 (s, 3H), 2.40–2.48 (m, 4H), 2.27 (m, 1H), 2.14 (m, 1H), 1.83–2.04 (m, 10H), 1.70 (m, 2H), 1.40 (t, 3H). HRMS $C_{37}H_{44}ClN_5O_4S$ *m/z* 690.2881 $(M+H)_{Cal.}$, 690.2901 $(M+H)_{Obs.}$.

Example 668

3-(1-(2,2-Dimethylpropanoyl)-4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-4-yl)phenol



tert-Butyl 4-(cyanomethyl)-4-(3-methoxyphenyl)piperidine-1-carboxylate was prepared using the same procedures used in Example 16a-d using 1-bromo-3-methoxybenzene in the place of 1-chloro-3-iodobenzene in Example 16b.

tert-Butyl 4-(3-methoxyphenyl)-4-(2-oxoethyl)piperidine-1-carboxylate. Using the same procedure as in Example 16e *tert*-butyl 4-(cyanomethyl)-4-(3-methoxyphenyl)piperidine-1-carboxylate (1.2 g, 3.8 mmol) gave *tert*-butyl 4-(3-

methoxyphenyl)-4-(2-oxoethyl)piperidine-1-carboxylate as a foam (0.9 g, 69%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.38 (t, 1H), 7.30 (m, 1H), 6.88–6.95 (m, 2H), 6.78 (m, 1H), 3.80 (s, 3H), 3.60 (m, 2H), 3.21–3.27 (m, 2H), 2.61 (s, 2H), 2.21 (m, 2H), 1.83 (m, 2H), 1.43 (s, 9H).

tert-Butyl 4-(3-methoxyphenyl)-4-{2-[3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidine-1-carboxylate. Using the same procedure as in Example 16f *tert*-butyl 4-(3-methoxy phenyl)-4-(2-oxoethyl)piperidine-1-carboxylate (0.9 g, 2.5 mmol) gave *tert*-butyl 4-(3-methoxyphenyl)-4-{2-[3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidine-1-carboxylate as a foam (1.2 g, 85%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (m, 1H), 7.28 (m, 2H), 7.16 (m, 2H), 6.88 (m, 2H), 6.76 (m, 1H), 4.62 (m, 1H), 3.82 (s, 3H), 3.65 (m, 2H), 3.16–3.26 (m, 4H), 3.08 (m, 1H), 2.58 (s, 3H), 2.37 (m, 2H), 2.13 (m, 2H), 1.83–1 97 (m, 6H), 1.78 (m, 3H), 1.61 (m, 2H), 1.43 (s, 9H).

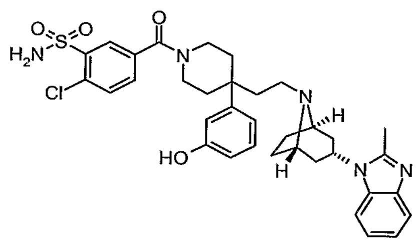
3-(4-{2-[3-(2-Methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-4-yl)phenol Hydrobromide. A mixture of *tert*-butyl 4-(3-methoxy phenyl)-4-{2-[3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidine-1-carboxylate (235 mg, 0.42 mmol) and 48% hydrobromic acid was heated at 100°C for 6 h. The mixture was concentrated and used without further purification.

3-(1-(2,2-Dimethylpropanoyl)-4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-4-yl)phenol (example 668). A mixture of 3-(4-{2-[3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-4-yl)phenol hydrobromide (0.22 g, 0.42 mmol), triethylamine (0.117 mL, 0.84 mmol) and trimethylacetyl chloride (0.057 mL, 0.462 mmol) in dichloromethane (2 mL) was stirred at rt for 3h. The reaction mixture was diluted with dichloromethane, washed with saturated sodium bicarbonate solution, dried, concentrated and purified by chromatography on silica gel eluting with 33:1 dichloromethane:methanol to give 3-(1-(2,2-dimethyl propanoyl)-4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-4-yl)phenol as a white solid (0.070 g, 32%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.25 (s, 1H), 7.47

(m, 1H), 7.34 (m, 1H), 7.05–7.15 (m, 3H), 6.77 (m, 1H), 6.73 (s, 1H), 6.59 (m, 1H), 4.51 (m, 1H), 3.74 (m, 2H), 3.24 (m, 4H), 2.47 (s, 3H), 2.36 (m, 2H), 1.97 (m, 2H), 1.86 (m, 4H), 1.75 (m, 6H), 1.58 (m, 2H), 1.15 (s, 9H). HRMS $C_{33}H_{44}N_4O_2$ *m/z* 529.3543 $(M+H)_{Cal.}$, 529.3542 $(M+H)_{Obs.}$.

Example 669

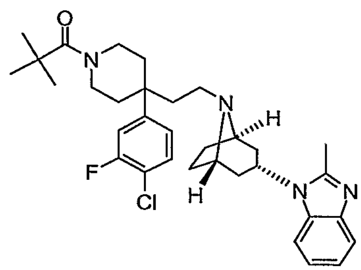
2-Chloro-5-[(4-(3-hydroxyphenyl)-4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)carbonyl]benzenesulfonamide



A mixture of 3-(4-{2-[3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl} piperidin-4-yl)phenol hydrobromide (0.25 g, 0.48 mmol), triethylamine (0.212 mL, 1.5 mmol) and 4-chloro-3-sulfamoylbenzoic acid (0.113 g, 0.48 mmol) in dimethylformamide (1.5 mL) was treated with O-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (0.2 g, 0.53 mmol) and the resulting mixture was stirred for 1 h at rt. The mixture was diluted with water and the resulting precipitate was collected, washed with saturated sodium bicarbonate solution and water, dried and purified by column chromatography on silica gel eluting with 200:15:1 chloroform:methanol:ammonium hydroxide to give 2-chloro-5-[(4-(3-hydroxyphenyl)-4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)carbonyl]benzenesulfonamide as a pink solid (0.022 g, 7%). ^{1}H NMR (400 MHz, CD_3OD) δ 8.08 (s, 1H), 7.67 (m, 1H), 7.60 (m, 1H), 7.51 (m, 1H), 7.41 (m, 1H), 7.18 (m, 3H), 6.84 (m, 2H), 6.67 (m, 1H), 4.74 (m, 1H), 4.15 (m, 1H), 3.54 (m, 1H), 3.32 (m, 7H), 2.52 (s, 3H), 2.34–2.50 (m, 3H), 2.20–2.30 (m, 1H), 1.78–2.10 (m, 10H), 1.65–1.72 (m, 2H). HRMS $C_{35}H_{40}ClN_5O_4S$ *m/z* 662.2568 $(M+H)_{Cal.}$, 662.2571 $(M+H)_{Obs.}$.

Example 670

1-((1R,5S)-8-{2-[4-(4-Chloro-3-fluorophenyl)-1-(2,2-dimethylpropanoyl)piperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1H-benzimidazole



tert-Butyl 4-(4-chloro-3-fluorophenyl)-4-(1-cyano-2-ethoxy-2-oxoethyl)piperidine-1-carboxylate. Using the same procedure as in Example 16b 1-bromo-4-chloro-5-fluorobenzene (10.7 g, 51 mmol) was used in place of 1-chloro-3-iodobenzene to give *tert*-butyl 4-(4-chloro-3-fluorophenyl)-4-(1-cyano-2-ethoxy-2-oxoethyl)piperidine-1-carboxylate as an amber foam that was used without further purification.

[1-(tert-Butoxycarbonyl)-4-(4-chloro-3-fluorophenyl)piperidin-4-yl](cyano)acetic Acid. *tert*-Butyl 4-(4-chloro-3-fluorophenyl)-4-(1-cyano-2-ethoxy-2-oxoethyl)piperidine-1-carboxylate was hydrolysed using the same procedure as in Example 16c to give [1-(*tert*-butoxycarbonyl)-4-(4-chloro-3-fluorophenyl) piperidin-4-yl](cyano)acetic acid as an amber solid that was used without further purification.

tert-Butyl 4-(4-chloro-3-fluorophenyl)-4-(cyanomethyl)piperidine-1-carboxylate. [1-(*tert*-Butoxycarbonyl)-4-(4-chloro-3-fluorophenyl)piperidin-4-yl](cyano)acetic acid was subjected to the same decarboxylation conditions used in Example 16d and chromatographed on silica gel eluting with a gradient of ethyl acetate:hexane 1:20 to 1:1 to give *tert*-butyl 4-(4-chloro-3-fluorophenyl)-4-(cyanomethyl)piperidine-1-carboxylate as a solid (2.3 g, 38% overall). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (m, 1H), 7.09–7.16 (m, 2H), 3.69–3.75 (m, 2H), 3.09 (m, 2H), 2.54 (s, 2H), 2.20-2.25 (m, 2H), 1.85 (m, 2H), 1.43 (s, 9H). ES-LCMS *m/z* 253 (M-99).

tert-Butyl 4-(4-chloro-3-fluorophenyl)-4-(2-oxoethyl)piperidine-1-carboxylate. Using the same procedure as in Example 16e *tert*-butyl 4-(4-chloro-3-fluorophenyl)-4-(cyanomethyl)piperidine-1-carboxylate (2.3 g, 6.5 mmol) gave *tert*-butyl 4-(4-chloro-3-fluorophenyl)-4-(2-oxoethyl)piperidine-1-carboxylate as an amber foam (1.5 g, 65%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.43 (t, 1H), 7.40 (m, 1H), 7.07–7.16 (m, 2H), 3.57–3.63 (m, 2H), 3.22–3.29 (m, 2H), 2.66 (s, 2H), 2.11–2.17 (m, 2H), 1.86 (m, 2H), 1.43 (s, 9H). ES-LCMS *m/z* 354 (M-1).

tert-Butyl 4-(4-chloro-3-fluorophenyl)-4-{2-[3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo [3.2.1]oct-8-yl]ethyl}piperidine-1-carboxylate. Using the same procedure as in Example 16f *tert*-butyl 4-(4-chloro-3-fluorophenyl)-4-(2-oxoethyl)piperidine-1-carboxylate (1.5 g, 4.2 mmol) gave *tert*-butyl 4-(4-chloro-3-fluorophenyl)-4-{2-[3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl} piperidine-1-carboxylate as a solid (1.4 g, 59%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (m, 1H), 7.38 (m, 1H), 7.28 (m, 1H), 7.17 (m, 2H), 7.02–7.09 (m, 2H), 4.66 (m, 2H), 3.83 (m, 2H), 3.62 (m, 2H), 3.23 (m, 4H), 3.01 (m, 1H), 2.60 (s, 3H), 2.43 (m, 2H), 1.65–2.01 (m, 10H), 1.43 (s, 9H). ES-LCMS *m/z* 581 (M+1).

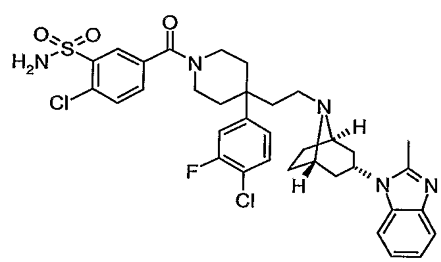
1-(8-{2-[4-(4-Chloro-3-fluorophenyl) piperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1H-benzimidazole dihydrochloride. Using the same procedure as in Example 16g *tert*-butyl 4-(4-chloro-3-fluorophenyl)-4-{2-[3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl} piperidine-1-carboxylate (1.4 g, 2.4 mmol) gave 1-(8-{2-[4-(4-chloro-3-fluorophenyl)piperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1H-benzimidazole dihydrochloride as a solid (1.4 g, 93%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.22 (s, 1H), 9.03 (s, 2H), 7.88 (m, 1H), 7.80 (m, 1H), 7.46–7.62 (m, 4H), 7.26 (m, 1H), 6.03 (m, 1H), 4.08 (m, 2H), 3.23 (m, 2H), 3.11 (m, 1H), 2.87 (s, 3H), 2.75–2.90 (m, 4H), 2.30 (m, 2H), 2.10–2.25 (m, 8H), 2.08 (m, 2H). ES-LCMS *m/z* 481 (M+1).

1-((1R,5S)-8-{2-[4-(4-Chloro-3-fluorophenyl)-1-(2,2-dimethylpropanoyl)piperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1H-benzimidazole (example 670). A mixture of 1-(8-{2-[4-(4-chloro-3-

fluorophenyl)piperidin-4-yl]ethyl}-8-azabicyclo [3.2.1]oct-3-yl)-2-methyl-1H-benzimidazole dihydrochloride (0.20 g, 0.39 mmol), triethylamine (0.11 mL, 0.78 mmol) and trimethylacetyl chloride (0.053 mL, 0.43 mmol) in dichloromethane (4 mL) was stirred at rt for 1 h before the reaction mixture was quenched with saturated sodium bicarbonate solution. The organic layer was separated, dried, concentrated and purified by chromatography on silica gel eluting with a dichloromethane to 1:9 methanol:dichloromethane gradient to give 1-((1R,5S)-8-{2-[4-(4-chloro-3-fluorophenyl)-1-(2,2-dimethylpropanoyl)piperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1H-benzimidazole as a white foam (0.11 g, 51%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (m, 1H), 7.40 (m, 1H), 7.29 (m, 1H), 7.03–7.19 (m, 4H), 4.72 (m, 1H), 3.90 (m, 2H), 3.33 (m, 4H), 2.59 (s, 3H), 2.42 (m, 2H), 1.78–2.13 (m, 14H), 1.27 (s, 9H). HRMS $C_{33}H_{42}ClFN_4O$ *m/z* 565.3109 $(M+H)_{Cal.}$, 565.3134 $(M+H)_{Obs.}$.

Example 671

2-Chloro-5-[(4-(4-chloro-3-fluorophenyl)-4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo [3.2.1]oct-8-yl]ethyl}piperidin-1-yl)carbonyl]benzene sulfonamide

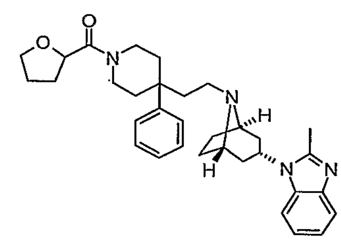


A mixture of 1-(8-{2-[4-(4-chloro-3-fluoro phenyl)piperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1H-benzimidazole dihydrochloride (0.40 g, 0.78 mmol), triethylamine (0.35 mL, 2.5 mmol) and 4-chloro-3-sulfamoylbenzoic acid (184 mg, 0.78 mmol) in dimethylformamide (2.5 mL) was treated with O-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (327 mg, 0.86 mmol) and the resulting mixture was stirred for 1 h at rt. The mixture was diluted with water and the resulting

precipitate was collected, washed with saturated sodium bicarbonate solution, with water, dried and purified by chromatography on silica gel eluting with a 400:15:1 to 200:15:1 gradient of chloroform:methanol:ammonium hydroxide to give 2-chloro-5-[(4-(4-chloro-3-fluoro phenyl)-4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)carbonyl]benzenesulfonamide as a solid (0.24 g, 43%). ^{1}H NMR (400 MHz, CD_3OD) δ 8.09 (s, 1H), 7.68 (m, 1H), 7.61 (m, 1H), 7.34–7.54 (m, 4H), 7.17–7.26 (m, 3H), 4.73 (m, 1H), 4.09 (m, 1H), 3.59 (m, 1H), 3.43 (m, 1H), 3.30 (m, 3H), 2.53 (s, 3H), 2.40–2.48 (m, 4H), 2.28 (m, 1H), 2.16 (m, 1H), 1.83–2.04 (m, 10H), 1.70 (m, 2H). HRMS $C_{35}H_{38}Cl_2FN_5O_3S$ *m/z* 698.2135 $(M+H)_{Cal.}$, 698.2142 $(M+H)_{Obs.}$.

Example 672

2-Methyl-1-((1R,5S)-8-{2-[4-phenyl-1-(tetrahydrofuran-2-ylcarbonyl)piperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-1H-benzimidazole

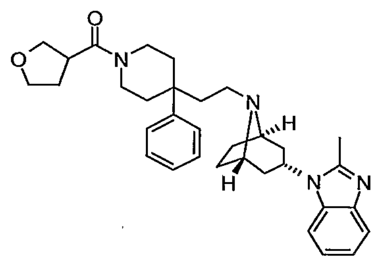


A mixture of 2-methyl-1-{8-[2-(4-phenylpiperidin-4-yl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1*H*-benzimidazole dihydrochloride (75 mg, 0.16 mmol), tetrahydro-2-furoic acid (18 mg, 0.16 mmol) and triethylamine (48 mg, 0.48 mmol) in dimethylformamide (0.5 mL) was treated with O-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (68 mg, 0.18 mmol) and the resulting mixture was stirred at rt for 1 h. The reaction mixture was diluted with water and the resulting precipitate was collected, washed with water and dried. The precipitate was triturated with a mixture of dichloromethane, methanol and hexane to give 2-methyl-1-((1R,5S)-8-{2-[4-phenyl-1-(tetrahydrofuran-2-ylcarbonyl)piperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-1H-benzimidazole as an off-white solid (0.017 g, 20%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.61–7.66 (m, 2H), 7.41 (m, 5H),

7.27–7.35 (m, 2H), 4.94 (m, 1H), 4.64 (m, 1H), 4.03 (m, 2H), 3.68–3.77 (m, 5H), 2.98–3.25 (m, 2H), 2.62–2.70 (m, 7H), 2.09–2.24 (m, 7H), 1.88–2.06 (m, 4H), 1.68–1.84 (m, 4H). HRMS $C_{33}H_{42}N_4O_2$ *m/z* 527.3386 $(M+H)_{Cal.}$, 527.3380 $(M+H)_{Obs.}$.

Example 673

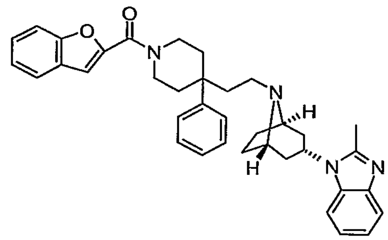
2-Methyl-1-((1R,5S)-8-{2-[4-phenyl-1-(tetrahydrofuran-3-ylcarbonyl)piperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-1H-benzimidazole



A mixture of 2-methyl-1-{8-[2-(4-phenyl piperidin-4-yl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1*H*-benzimidazole dihydrochloride (75 mg, 0.16 mmol), tetrahydro-3-furoic acid (18 mg, 0.16 mmol) and triethylamine (48 mg, 0.48 mmol) in dimethylformamide (0.5 mL) was treated with O-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (68 mg, 0.18 mmol) and the resulting mixture was stirred at rt for 1h. The reaction mixture was diluted with water and extracted with dichloromethane. The residue from the dichloromethane layer was purified by chromatography on silica gel eluting with 1:20 methanol:dichloromethane to give 2-methyl-1-((1R,5S)-8-{2-[4-phenyl-1-(tetrahydrofuran-3-ylcarbonyl)piperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-1H-benzimidazole as a clear oil (0.019 g, 23%). ^1H NMR (400 MHz, DMSO-d_6) δ 7.46 (m, 1H), 7.36 (m, 5H), 7.21 (m, 1H), 7.09 (m, 2H), 4.49 (m, 1H), 3.58–3.87 (m, 7H), 3.12–3.35 (m, 6H), 2.28–2.39 (m, 2H), 1.89–2.12 (m, 5H), 1.58–1.86 (m, 10H), 1.53–1.60 (m, 2H). HRMS $C_{33}H_{42}N_4O_2$ *m/z* 527.3386 $(M+H)_{Cal.}$, 527.3397 $(M+H)_{Obs.}$.

Example 674

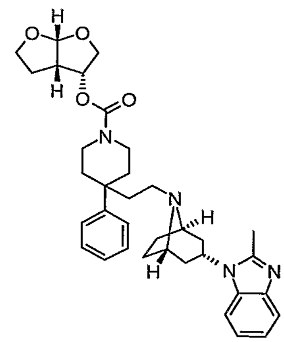
1-((1R,5S)-8-{2-[1-(1-Benzofuran-2-ylcarbonyl)-4-phenylpiperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1H-benzimidazole



A mixture of 2-methyl-1-{8-[2-(4-phenyl piperidin-4-yl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1*H*-benzimidazole dihydrochloride (100 mg, 0.22 mmol), 2-benzofurancarboxylic acid (36 mg, 0.22 mmol) and triethylamine (66 mg, 0.66 mmol) in dimethylformamide (0.75 mL) was treated with O-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (92 mg, 0.24 mmol) and the resulting mixture was stirred at rt for 1h. The reaction mixture was diluted with water and the resulting precipitate was collected, washed with water and dried. The precipitate was purified by chromatography on silica gel eluting with 1:20 methanol:dichloromethane to give 1-((1R,5S)-8-{2-[1-(1-benzofuran-2-ylcarbonyl)-4-phenylpiperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1H-benzimidazole as a clear oil (0.075 g, 60%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (m, 2H), 7.52 (m, 1H), 7.26–7.44 (m, 9H), 7.16 (m, 2H), 4.61 (m, 1H), 4.16 (m, 2H), 3.40–3.57 (m, 2H), 3.26 (m, 1H), 2.57 (m, 3H), 2.34 (m, 4H), 1.94 (m, 9H), 1.62 (m, 4H). HRMS $C_{37}H_{40}N_4O_2$ *m/z* 573.3229 $(M+H)_{Cal.}$, 573.3238 $(M+H)_{Obs.}$.

Example 675

(3R,3aS,6aR)-Hexahydrofuro[2,3-b]furan-3-yl 4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo [3.2.1]oct-8-yl]ethyl}-4-phenylpiperidine-1-carboxylate

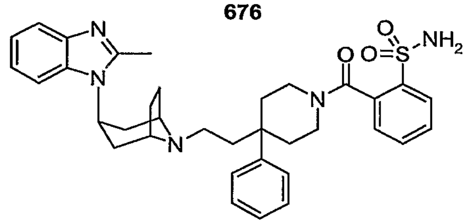


A mixture of 2-methyl-1-{8-[2-(4-phenyl piperidin-4-yl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1*H*-benzimidazole dihydrochloride (100 mg, 0.22 mmol), (3*R*,3a*S*,6a*R*)-hexahydrofuro[2,3-*b*]furan-3-yl 4-nitrophenyl carbonate (78 mg, 0.26 mmol) and N,N-diisopropylethylamine (0.15 mL, 0.88 mmol) in acetonitrile (3 mL) was stirred at rt for 16 h. The reaction mixture was concentrated and the residue in dichloromethane was washed with saturated sodium carbonate solution, dried, concentrated and chromatographed on silica gel eluting with 1:40 methanol:dichloromethane to give (3R,3aS,6aR)-hexahydrofuro[2,3-b]furan-3-yl 4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidine-1-carboxylate as a clear glass (0.064 g, 50%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (m, 2H), 7.29 (m, 5H), 7.16 (m, 2H), 5.71 (m, 1H), 5.18 (m, 1H), 4.59 (m, 1H), 3.75–4.04 (m, 7H), 3.22 (m, 3H), 3.05 (m, 1H), 2.58 (m, 3H), 2.19–2.36 (m, 4H), 1.80–1.92 (m, 9H), 1.61 (m, 5H). HRMS $C_{35}H_{44}N_4O_4$ *m/z* 585.3441 $(M+H)_{Cal.}$, 585.3440 $(M+H)_{Obs.}$.

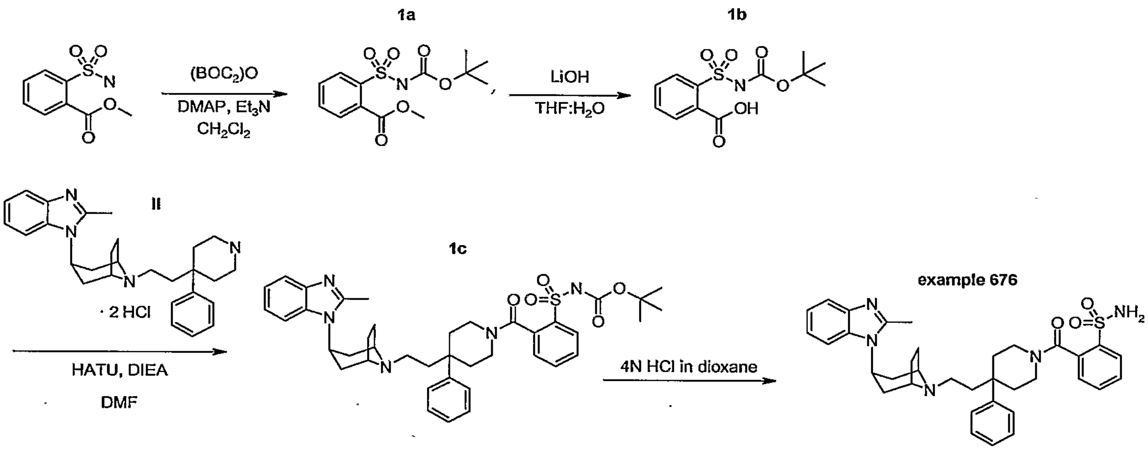
Example 676

2-[(4-{2-[3-(2-Methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]benzenesulfonamide

676



Example 676 was prepared as outlined below.



Methyl 2-{[(tert-butoxycarbonyl)amino] sulfonyl}benzoate 1a. A mixture of methyl 2-(aminosulfonyl)benzoate (500 mg, 2.3 mmol, 1 eq.), triethylamine (320 µL, 2.3 mmol, 1 eq.), 4-(dimethylamino)pyridine (281 mg, 2.3 mmol, 1 eq.) and di(*tert*-butyl) dicarbonate (1.0 g, 4.6 mmol, 2 eq.) in dichloromethane (20 mL) was stirred at RT for 2 h. The reaction was concentrated and the residue partitioned between dichloromethane and saturated ammonia chloride. The organic layer was dried and concentrated, and the residue purified by column chromatography on silica gel eluting with 1:1 hexane:ethyl acetate to afford methyl 2-{[(tert-butoxycarbonyl)amino]sulfonyl}benzoate (1a) as a white solid (326 mg, 45% yield). ^{1}H NMR (300 MHz, DMSO) δ 11.71 (s, 1H), 8.00 (m, 1H), 7.75 (m, 2H), 7.67 (m, 1H), 3.83 (s, 3H), 1.27 (s, 9H). ES-LCMS *m/z* 314.16 (M-H).

2-{[(tert-butoxycarbonyl)amino]sulfonyl} benzoic acid 1b. A mixture of methyl 2-{[(tert-butoxycarbonyl)amino]sulfonyl}benzoate 1a (400 mg, 1.3 mmol, 1 equiv) and lithium hydroxide (1.6 g, 39 mmol, 30 equiv) in tetrahydrofuran (10 mL) and water (2.5 mL) was stirred at RT for 18 h. The reaction was partially concentrated, acidified with 1N HCl and the product extracted into ethyl acetate. The organic layer was dried and concentrated to afford 2-{[(tert-butoxy carbonyl)amino]sulfonyl}benzoic acid (1b) as a white solid (200 mg, 51% yield). ^{1}H NMR (300 MHz, DMSO) δ 7.94 (m, 1H), 7.71 (m, 3H), 1.26 (s, 9H). ES-LCMS *m/z* 300.08 (M-H).

tert-Butyl {2-[(4-{2-[3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]phenyl}sulfonyl carbamate, 1c. To a solution of *endo* 2-methyl-1-{8-[2-(4-phenylpiperidin-4-yl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1*H*-benzimidazole dihydrochloride II (238 mg, 0.47 mmol, 1 eq.) in dimethylformamide (14 mL) was added 2-{[(tert-butoxycarbonyl)amino]sulfonyl}benzoic acid 1b (140 mg, 0.47 mmol, 1 eq.) and *N,N*-diisopropylethyl amine (0.3 mL, 1.41 mmol, 3 eq.). After stirring at RT for several minutes, *O*-(7-azabenzotriazol-1-yl)-*N N,N', N'*-tetramethyluroniumhexafluorophosphate (179 mg, 1.41 mmol, 1 eq.) was added and the reaction was stirred for 2 h. The mixture was partitioned between dichloromethane and water. The organic layer was dried and concentrated to provide crude *tert*-butyl {2-[(4-{2-[3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1] oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]phenyl} sulfonylcarbamate 1c. The crude product was used without further purification.

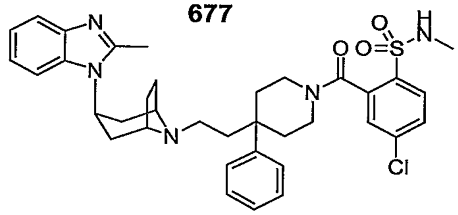
2-[(4-{2-[3-(2-Methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]benzenesulfonamide (example 676). A mixture of crude *tert*-butyl {2-[(4-{2-[3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]phenyl}sulfonyl carbamate 1c and 4N HCl in dioxane (3 mL) was stirred at RT for 2 h. The reaction mixture was partitioned between dichloromethane and saturated aqueous sodium bicarbonate. The organic layer was dried and concentrated and the residue was purified by prep. HPLC (Method Y) to provide 2-[(4-{2-[3-

(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]benzenesulfonamide 1 as a white solid (45 mg, 16% yield). ^{1}H NMR (300 MHz, DMSO) δ 8.05 (m, 1H), 7.63 (m, 3H), 7.39–7.15 (m, 9H), 5.61 (m, 2H), 4.60 (m, 1H), 4.38 (m, 1H), 3.43–3.04 (m, 5H), 2.54 (s, 3H), 2.35–2.17 (m, 4H), 2.13–1.40 (m, 12H). ES-LCMS *m/z* 612.25 (M+H). Analytical HPLC (Method W) Rt 7.59 (95.89%).

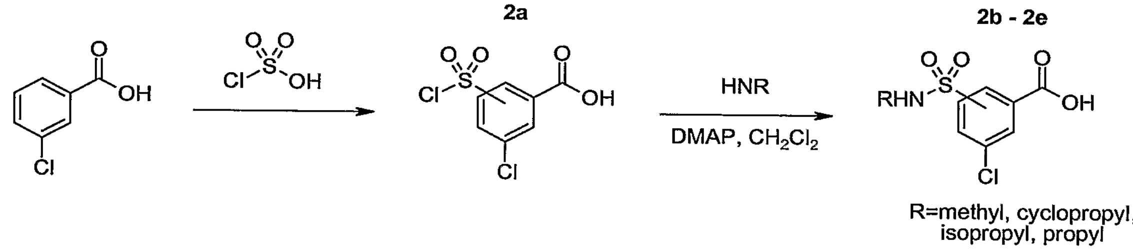
Example 677

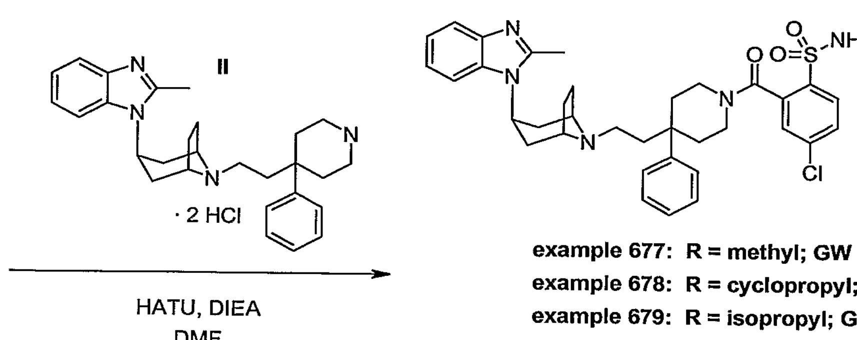
4-Chloro-N-methyl-2-[(4-{2-[3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]benzenesulfonamide

677



Example 677 was prepared as outlined below.

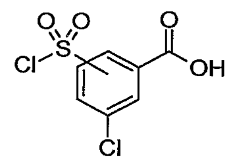




example 677: R = methyl; GW 854583X
example 678: R = cyclopropyl; GW 854584X
example 679: R = isopropyl; GW 854585X
example 680: R = propyl; GW 854586X

A mixture of 3-chloro-4-(chlorosulfonyl) benzoic acid and 5-chloro-2-(chlorosulfonyl)benzoic acid, 2a.

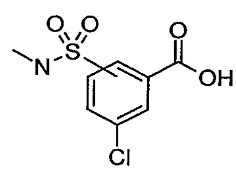
2a



3-Chlorobenzoic acid (7.0 g, 44.7 mmol, 1 equiv) was added at 0 °C to chlorosulfonic acid (40 mL). The reaction mixture was heated to 120 °C for 72 h, cooled to RT and poured slowly over ice. The product was extracted into diethyl ether, dried and concentrated to provide a 4:1 mixture of regioisomers, 5-chloro-4-(chlorosulfonyl)benzoic acid and 3-chloro-2-(chlorosulfonyl)benzoic acid 2a as a brown solid (5.26 g, 46% yield). ^{1}H NMR (300 MHz, DMSO) δ 8.07 (m, 1H), 7.96 (m, 1H), 7.79 (m, 3 H), 7.59 (m, 1H). ES-LCMS m/z 234.85 (M-2H) for $C_7H_5ClO_5S$.

A mixture of 5-chloro-2-[(methylamino) sulfonyl]benzoic acid and 3-chloro-4-[(methylamino) sulfonyl]benzoic acid, 2b.

2b



To a solution of 3-chloro-4-(chlorosulfonyl)benzoic acid and 5-chloro-2-(chlorosulfonyl)benzoic acid 2a (0.5 g, 1.96 mmol, 1 eq.) in dichloromethane (10 mL) was added 4-(dimethylamino)pyridine (24 mg, 0.196 mmol, 0.1 eq.) and 2M methyl amine in THF (2.94 mL, 5.88 mmol, 3 eq.). The reaction mixture was stirred at RT for 18 h then concentrated to dryness. The residue was acidified with 1N HCl and the product was extracted into dichloromethane. The organic layer was concentrated, the residue taken up in water and acidified with 1N HCl. The product was extracted into dichloromethane, dried and concentrated to provide a crude mixture of 5-chloro-2-[(methylamino)sulfonyl] benzoic acid and 3-chloro-4-

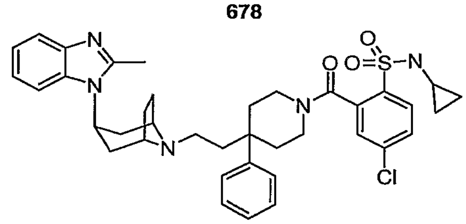
[(methylamino)sulfonyl] benzoic acid 2b. The residue was carried on without further purification. ES-LCMS m/z 248.01 (M-H).

4-Chloro-N-methyl-2-[(4-{2-[3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]benzenesulfonamide (example 677). The title compound was prepared from a mixture of 5-chloro-2-[(methylamino)sulfonyl]benzoic acid and 3-chloro-4-[(methylamino)sulfonyl]benzoic acid 2b and endo 2-methyl-1-{8-[2-(4-phenylpiperidin-4-yl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1H-benzimidazole dihydrochloride II following the general procedure for tert-butyl {2-[(4-{2-[3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenyl piperidin-1-yl)carbonyl]phenyl}sulfonylcarbamate 1c. The desired regioisomer was purified by column chromatography on silica gel eluting with 10% methanol in ethyl acetate to afford 4-chloro-N-methyl-2-[(4-{2-[3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1] oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]benzene sulfonamide 2 as a white solid (15 mg, 8% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (d, 1H, J=7.9 Hz), 7.65 (m, 1H), 7.53 (m, 1H), 7.39 (m, 3H), 7.27 (m, 4H), 7.19–7.12 (m, 2 H), 5.12 (q, 1H, J=5.2 Hz), 4.60 (m, 1H), 4.20 (m, 1H), 3.48–3.20 (m, 5H), 2.64 (d, 3H, J=5.3 Hz), 2.56 (s, 3H), 2.40–2.33 (m, 3H), 2.18 (m, 1H), 1.93–1.62 (m, 12H). ES-LCMS m/z 662.30 (M+2H). Analytical HPLC (Method Y) Rt 4.16 (90.0%).

Example 678

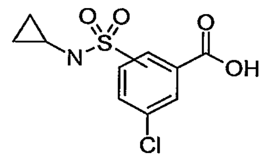
4-Chloro-N-cyclopropyl-2-[(4-{2-[3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]benzenesulfonamide

678



A mixture of 5-chloro-2-[(cyclopropylamino) sulfonyl]benzoic acid and 3-chloro-4-[(cyclopropyl amino)sulfonyl]benzoic acid, 2c.

2c



The mixture was prepared from a mixture of 3-chloro-4-(chlorosulfonyl)benzoic acid and 5-chloro-2-(chloro sulfonyl)benzoic acid 2a and cyclopropyl amine following the general procedure for 5-chloro-2-[(methyl amino)sulfonyl]benzoic acid and 3-chloro-4-[(methyl amino)sulfonyl]benzoic acid 2b. The crude reaction mixture was carried on without further purification.

ES-LCMS m/z 274 (M-H).

4-Chloro-N-cyclopropyl-2-[(4-{2-[3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]benzene sulfonamide (example 678). The title compound was prepared from a mixture of 5-chloro-2-[(cyclopropyl amino)sulfonyl]benzoic acid and 3-chloro-4-[(cyclo propylamino)sulfonyl]benzoic acid 2c and endo 2-methyl-1-{8-[2-(4-phenylpiperidin-4-yl)ethyl]-8-azabicyclo [3.2.1]oct-3-yl}-1H-benzimidazole dihydrochloride II following the general procedure for tert-butyl {2-[(4-{2-[3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo [3.2.1]oct-8-yl]ethyl}-4-phenyl piperidin-1-yl)carbonyl]phenyl}sulfonylcarbamate 1c. The desired regioisomer was purified by column chromatography on silica gel eluting with 10% methanol in ethyl acetate to afford 4-chloro-N-cyclopropyl-2-[(4-{2-[3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo [3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl] benzene sulfonamide 3 as a white solid (15 mg, 11% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (d, 1H, J=8.1 Hz), 7.65 (m, 1H), 7.54 (m, 1H), 7.41–7.12 (m, 9H), 5.48 (s, 1H), 4.60 (m, 1H), 4.20 (m, 1H), 3.45–3.23 (m, 6H), 2.56 (s, 3H), 2.40–2.33 (m, 3H), 2.20–2.17 (m, 1H), 1.97–1.58 (m, 10H), 0.70–0.56 (m, 4H). ES-LCMS m/z 688.35 (M+2H). Analytical HPLC (Method Y) Rt 3.34 (89.34%).